University of Alberta

Modifiable Risk Factors for Invasive Meningococcal Disease, Edmonton, Alberta, 1999-2002: A Case-Control Study

by

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I dedicate this work to my mother—

Thanks for always being such a great support

Abstract

An outbreak of invasive meningococcal disease (IMD) in the Capital Health region (metro Edmonton, Alberta) between December 1999 and June 2002 resulted in 84 laboratory-confirmed cases. Most cases (89%) were infected with *Neisseria meningitidis* serogroup C, and the highest age-specific incidence was observed in the 15 to 19 year age cohort (32% of cases). A case-control study was conducted to identify modifiable IMD risk factors among outbreak cases. Controls were recruited through random-digit dialing, and matched to cases on age and gender. A questionnaire was telephone-administered to 132 study participants (44 cases, 88 controls). Conditional logistic regression was utilized to calculate risk measures. Multivariate analysis revealed three statistically significant risk factors (bar patronage, "rave" attendance, maternal smoking) and one protective factor (humidifier use in the home). While the precision of risk estimates was low in the multivariate model, this study has identified rave attendance as an emergent IMD risk factor.

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List of Abbreviations

CATI = computer assisted telephone interviewing

CDN = Canadian

CSF = cerebrospinal fluid

ET = electrophoretic type

HIV = human immunodeficiency virus

HREB = Health Research Ethics Board

IMD = invasive meningococcal disease

OR = odds ratio

PCR = polymerase chain reaction

PRL = Population Research Laboratory

RHA = regional health authority

URTI = upper respiratory tract infection

CHAPTER 1: BACKGROUND AND STUDY RATIONALE

1.1 Invasive Meningococcal Disease—Clinical Aspects and Global Epidemiology

Invasive meningococcal disease (IMD) is a communicable infection caused by the bacterium *Neisseria meningitidis*. Worldwide, it is the leading cause of epidemic meningitis and fatal septicemia.[1] An estimated 1.2 million cases occur each year globally, with the highest incidence observed in 18 sub-saharan African nations (known as the "meningitis belt"); IMD rates in excess of 250 cases/100,000 are often seen during periodic epidemics in this region.[2] In recent decades, the incidence of IMD in most industrialized nations has been far lower, approximately 1-3/100,000.[3] In Canada, while IMD incidence rates were low (between 0.70-1.13/100,000) between 1999 and 2001, eight IMD outbreaks were observed nationally during this time period.[4] The largest of these outbreaks, on which this research is based, occurred in Edmonton, Alberta.

Exposure to respiratory droplets of a *N. meningitidis* carrier, subsequent infection, and invasion of the nasopharynx are necessary for IMD to occur, with each step mediated by multiple factors.[5] Meningococcal bacteria are spread from person-to-person through direct contact with or inhalation of respiratory droplets containing viable *N. meningitidis* from human carriers, the only natural reservoir for the organism.[6] Infection usually occurs two to ten days (mean three to four days) after exposure to the bacterium.[7] Asymptomatic nasopharyngeal colonization is common, and while colonization rates are variable, it has been estimated that approximately 10% of the population carries meningococcal bacteria.[8,9] Invasion of nasopharyngeal mucosal cells (and passage into the bloodstream) occurs in only a small fraction of those infected, as not all meningococcal strains are pathogenic, previous colonization can act as an "immunizing" process, and host defences usually prevent invasive disease.[10] Colonization rates, then, are a reflection of conditions favorable for the transmission of IMD, rather than a marker for an outbreak of the disease in the population.[6]

Clinically, IMD usually manifests as meningitis (meningococcal meningitis), and/or septicemia (meningococcemia). These syndromes account for approximately 50 and 20 percent of IMD cases respectively, and taken together, have a mortality rate of approximately 10%; in another approximately 10% of cases, serious sequelae result, including hearing impairment, neurological disability, and loss of digits/limbs.[11] Meningococcal meningitis presents similarly to other forms of bacterial meningitis, with sudden onset of intense headache, fever, nausea, vomiting, stiff neck and in some cases delirium.[7] Meningococcemia is the more clinically severe form of the illness. The condition, characterized by a petechial skin rash, can rapidly progress to hemodynamic collapse and multisystem organ failure, and death (the case fatality rate for meningococcemia is often greater than 20%) can occur within 12 hours of initial onset.[12]

1.2 Invasive Meningococcal Disease Molecular Epidemiology and Vaccines

N. meningitidis is sub-classified into 13 distinct serogroups, based on distinct polysaccharides present in the bacterial capsule,[10] which is significant from both an epidemiologic and disease prevention standpoint. The distribution of meningococcal serogroups varies geographically and temporally. Serogroups B and C are responsible for most IMD in Europe and North America, while in Asia and Africa, groups A and C predominate.[3] In Canada groups A and C were most frequently identified prior to 1975; between 1975 and 1989, group B predominated, after which group C was observed with increasing incidence[13] (by 2000 and 2001, the majority of meningococcal isolates were group C).[4] Recent changes in serogroup incidence have also been observed in the U.S.[14] and Europe.[15]

The capsular polysaccharide is an important virulence factor (isolates lacking the capsule are non-pathogenic), and five serogroups, A, B, C, Y and W-135, cause virtually all cases of IMD.[16] It is also the capsular polysaccharides of these five serogroups that have been used in the development IMD vaccines.[17] However, the antigenic properties of these serogroups have made the development of universally effective and long-lasting meningococcal vaccines elusive. This is reflected in current Health Canada guidelines on the recommended use of meningococcal vaccines,[18] a partial summary of which follows. IMD immunization is the primary method of control of IMD in high-risk groups, mainly those less than 19 years of age, the age stratum in which more than half of IMD cases are reported. "Polysaccharide" vaccines (those containing purified meningococcal capsular polysaccharide) are available for serogroups A, C, Y and W-135. However, these vaccines confer relatively short-term immunity (less than three years),[19] have reduced efficacy in children less than ten years of age, and are ineffective in children less than two years of age. The group B polysaccharide is poorly immunogenic, and thus there is currently no licensed vaccine available for this serogroup. Recently, vaccines containing meningococcal polysaccharides chemically conjugated to a protein carrier ("conjugate" vaccines) have been licensed in Canada. These provide longer-term immunity (as the carrier protein elicits a t-cell response), and are effective for all age groups. However, only group A and C conjugate vaccines have been developed, and only group C vaccines are currently marketed.

1.3 Invasive Meningococcal Disease Surveillance in Alberta, Canada

IMD is a reportable disease in Alberta. That is, report of each case confirmed by a laboratory and/or physician must be provided by "fastest means possible" to the Medical Officer of Health of the region in which the case resides, which in turn must be reported to the Chief Provincial Health Officer, as per provincial regulations.[20] This facilitates surveillance of IMD, both regionally and provincially. When sporadic cases of IMD are reported in Alberta, regional public health agencies work to reduce the spread of infection through administration of chemoprophylaxis (antibiotics, usually rifampin) to close contacts of the case, as per Health Canada recommendations.[21] In late 1999 a significant increase in IMD incidence was detected in the Capital Health region among individuals with no known epidemiologic link, and thus other methods of control were explored.[22]

1.4 Outbreak of Invasive Meningococcal Disease in the Capital Health Region, Alberta

Between December 1999 and June 2002, an outbreak of IMD (of more than 80 cases) occurred in the Capital Health region (metro Edmonton), Alberta, Canada. IMD surveillance information collected and public health measures undertaken during the outbreak,[22] as well as the molecular epidemiology of the outbreak,[23] is summarized elsewhere. A brief summary of these previously published reports as relevant to this research is presented here. A description of the outbreak case series will be presented as part of this research later in the report.

Between December 1999 and February 2000, the rate of IMD in those aged 15 to 19 years of age in the Capital Health region (see regional map in Section 3.3 of this report) rose dramatically, and reached ten per 100,000 during the three-month period. In the 20 years prior to the outbreak, the average annual IMD incidence rate in Alberta was one per 100,000. This cluster was deemed to have met a widely accepted definition of a community IMD outbreak,[24] and immunization of those at increased risk is a management strategy recommended by Health Canada when outbreaks of vaccine-preventable serogroups are identified.[21] Most cases were infected with *N. meningitidis* serogroup C (vaccine-preventable), and thus, the cluster elicited a mass immunization campaign for the 15-19 year age cohort in the region. Due to heightened public concern and subsequent increased IMD incidence in other age cohorts, a total of six immunization campaigns targeting those aged two to 24 years of age were executed between February 2000 and March 2002. Approximately 86% of the 250,000 residents of the region eligible to receive the vaccine was immunized during the campaigns. IMD incidence returned to pre-outbreak rates after June 2002.

The formats of vaccine administered varied during the campaign, based on vaccine availability and the licensing of new vaccines. For most of the campaigns, only polysaccharide vaccines were available. Two different polysaccharide vaccines were used (based on availability), containing polysaccharides from four (A, C, Y, W-135) or two (A, C) serogroups. Significant IMD rates were observed in infants less than one year of age during the outbreak. However, polysaccharide vaccines are ineffective (and therefore not licensed for use) in those less than two years of age, and thus were not administered to this cohort. In April 2001, a new conjugate vaccine protective against serogroup C was licensed in Canada. In September 2001, the vaccine was made available to residents of the Capital Health region two to 23 months of age, and on April 1, 2002, this vaccine was added to the routine Alberta childhood immunization schedule.

1.5 Study Rationale

As outlined in the previous sub-section, IMD causes significant morbidity and mortality worldwide, and Public Health agencies have endeavored to reduce the incidence of the infection. Tracing and chemoprophylaxis of contacts as well as immunization programs have been used in this regard. These prevention and control measures, while generally successful, have inherent limitations that impact their feasibility and effectiveness. Administration of antibiotics (such as rifampin) to close contacts of IMD cases has helped to reduce incidence within this risk group.[14] However, this control measure is not adequate for control of community outbreaks. Chemoprophylaxis would likely be ineffective (as exposure to the infectious agent is prolonged and from multiple sources during outbreaks, and few cases occur as a result of contact with another known case) and impractical (as a result of the relatively high cost and logistical issues) in such situations.[11] While relatively rare, rifampin-resistant *N. meningitis* isolates have been observed,[25] which may also impact the effectiveness of this control measure in the future.

As introduced above, immunization against IMD, the primary means of prevention among groups at higher risk, has limitations that are associated with the characteristics of the vaccines currently available and the epidemiology of IMD. The expense and public health effort required for mass immunization in the control of a relatively rare infection are a consideration,[24] and thus the vaccine is not routinely offered in many jurisdictions. As well, there is currently no licensed vaccine available in Canada for serogroup B, which until 1999 was the most frequently observed serogroup among IMD cases in Canada. Group B vaccines have been used in Europe and Latin America, however, geographic and temporal variation of some group B antigens, as well as the theoretical risk of autoimmunity when other group B antigens are used in vaccine production, present challenges in developing effective group B vaccines.[11] Polysaccharide vaccines for other common IMD serogroups, as discussed, provide only short-term immunity, and are of reduced or no effectiveness in certain age cohorts of children, the most important risk group. Conjugate vaccines, a universally effective format, are currently marketed only for group C. While this is currently the most common serogroup in Canada, the molecular epidemiology of IMD is variable, and it would seem probable that the incidence of serogroups for which there are vaccines of only limited effectiveness may increase in the future.

The serious clinical effects of IMD, and the limitations of control measures currently used by public health agencies for this infection, make it worthwhile to explore other possible methods of prevention. Identification of modifiable IMD risk factors is an important step in this regard. The identification of such factors could lead directly to a reduction in IMD incidence, through the implementation of strategies to mitigate identified risks, or indirectly, by helping to identify those in the population at increased risk for effective targeting of immunization or other prophylaxis measures.

CHAPTER 2: LITERATURE REVIEW

2.1 Non-modifiable Risk Factors for Invasive Meningococcal Disease

IMD surveillance has identified important non-modifiable risk factors, which must considered in the identification of other risk factors. As discussed, certain age cohorts (i.e. less than five years of age and 15-19 years of age) are clearly at higher risk.[16] Sex may play a role in IMD risk, as evidenced by documented significant differences in age distribution among male and female IMD cases.[4] Contact with a known IMD case has been demonstrated to increase risk.[11] Deficiencies in host immune status, including those caused by complement disorders[26] and asplenia[27] may also increase the risk. Environmental factors such as seasonal low rainfall and humidity can be an important predictor of IMD outbreaks, especially in Africa's meningitis belt.[28] However, several modifiable risk factors (that is, factors that can be altered to reduce the risk), in addition to IMD immunization status, have also been studied. The identification of such risk factors may help to reduce IMD incidence either directly, through reduction of identified risk factors, or indirectly, by targeting currently used control strategies (such as chemoprophylaxis) to those groups more likely to have these factor(s). The body of scientific literature describing modifiable IMD risk factors is summarized here.

2.2 Modifiable Risk Factors for Invasive Meningococcal Disease

A review of the literature was conducted to identify modifiable IMD risk factors, with the following search strategy: search of the PubMed Medline electronic database with keywords "invasive meningococcal disease" or "meningococcal meningitis" or "meningococcemia" or "bacterial meningitis", and "risk". Articles were selected if written in English, and if the research methods used to identify risk factor(s) were consistent with published validity guides for medical literature.[29] Articles regarding IMD immunization status as a risk factor are not included in this review, nor are articles describing risk factors for asymptomatic colonization with meningococcal bacteria. Sixteen key studies were identified in this search, individually reviewed in Appendix A. A summary of the risk factors identified in this research follows.

Several modifiable IMD risk factors have been identified in the literature. Exposure to tobacco smoke, both passive[30-39] and active,[40] is identified as a risk factor in most of the key studies.

Children with a mother,[31,33,37] father[33] or primary caregiver[38] that smokes also appear to be at greater risk for IMD. Varied indices of household crowding[30-32,35,36,39,42] and specifically, residence in student housing on college campuses,[43] sharing of a bedroom[34,38] (with an IMD case)[44] have also been a frequently observed risk factor. Other dwelling characteristics, such as method of heating[43] indoor dust/particulate exposure[30,34,44] and use of a humidifier (protective)[31] have also been cited as risk factors. Antecedent upper respiratory illness[32,39,41,43] (and specifically, influenza)[45] has been identified as increasing IMD risk. Group activities outside the home (substantial social gatherings,[32] bar patronage)[40] added to the risk, however, church attendance was reported as being protective.[31] Other identified risk factors include stressful life events,[30] oral muscle tone deficiency (i.e. speech pathology or snoring),[34] intra/international travel,[30] socio-economic status[30] and race.[43] In children, maternal education,[31] age at which breastfeeding was stopped[39] and day care attendance (protective)[35] appear to be significant IMD risk factors.

Most key studies were observational (population-based case-control) and initiated retrospectively as a result of local outbreaks or nationwide epidemics of IMD that occurred globally between the late 1980s and late 1990s. Among the earliest of this research included studies conducted in the United Kingdom[30,45] and Chad.[41] Studies with similar designs were carried out in Ghana,[44] South Africa,[39] New Zealand,[32] the U.S.[31, 40] and elsewhere in Europe[33,35,36] in the following several years, after outbreaks or epidemics in those jurisdictions. Two case-control studies were carried out in Australia[34,38] in the mid- and late 1990s that were not in response to epidemics. One U.S.-based cohort[37] and two nested case-control studies (in the U.S.[43] and Denmark)[42] were carried out, generally utilizing larger populations and/or longer study periods rather than outbreak clusters as the source of IMD case participants.

Data collection methods and type of risk estimate reported were similar among most of the key studies, as these were appropriate for the study designs employed and the nature of the risk factors under investigation. Survey methods (interviewer-administered questionnaires) were used in most of the key studies for collection of risk factor information. Clinical specimens (blood,[45] nasopharyngeal washings)[41] were collected for two research studies in which the association between IMD and antecedent respiratory infections was primarily being examined. Registry data (birth certificate database,[37] national registry database)[42,43] were used for collection of risk factor information in two of the key studies. Risk estimates were mainly reported as odds ratios. The point estimates for significant risk associations were generally in range of OR=2.0 – 4.0, with relatively wide 95% confidence intervals, a function of the small sample size for most of the key studies.

IMD immunization status was not a consideration in assessing risk in most of the key studies, as the vaccine was not available to the population under study, or, study cases were infected with an IMD serogroup for which there was no licensed vaccine. Two key studies[40,43] focused on U.S. college students, who in some instances had been offered IMD vaccine as a result of serogroup C IMD outbreaks in that population. The first of these studies included students from two colleges to whom IMD vaccine had been offered as a result of an IMD outbreak; however, all outbreak cases had onset prior to the immunization campaign, and thus controlling for immunization status was not necessary in the control group. The second was a nationwide prospective surveillance/nested case-control study of U.S. college students; the large study population allowed for immunized individuals to be excluded from participation. The initiation of an immunization campaign early in the Edmonton outbreak, and the high immunization rate among high-risk age groups in the study population meant that immunization status had to be carefully considered in this research, as will be described later.

2.3 Limitations of Key Invasive Meningococcal Disease Risk Factor Studies

There are several limitations generally applicable to the key IMD modifiable risk factor studies. The IMD case definition varied among the studies; some used only laboratory confirmed cases, while others included clinical cases. The inclusion of cases for which the diagnosis was not laboratory confirmed may have introduced case ascertainment bias. Most of the key research studied specific age cohorts with relatively high IMD incidence (i.e. young children or young adults), rather than the entire population. As well, varying criteria were used when assessing exposure to various risk factors. For example, the operational definitions for passive environmental tobacco smoke exposure and household density/crowding varied considerably among the studies in which these factors were considered. These discrepancies impact the comparability of the studies as a body of research.

Most IMD studies in which modifiable risk factors have been examined are also relatively small in size. This may be a result of the nature of the study populations used in most of the studies; most were within developed nations (i.e. Europe, Australia and the United States), where IMD rates are relatively low. The study designs used in this body of research have also generally been observational (case-control). Such designs were likely chosen both as a result of the rarity of IMD in the study populations, and the ethical and practical considerations in assigning potentially harmful exposures to study participants in preferred designs (i.e. randomized control trials). The challenge in these designs is to ensure similarity in all known determinants of outcome (i.e. development of IMD) in the case and control/reference group.[29] In most of the key studies, the researchers attempted to stratify out differences in the study groups through matching (by age, sex and/or area) and/or statistical adjustment (multivariate analysis). However, as other researchers have described,[42] the adjustment for social confounders in several of the key studies may have been incomplete.

2.4 Summary of Lower Validity Invasive Meningococcal Disease Modifiable Risk Factor Studies

Several IMD modifiable risk factor studies did not sufficiently conform to key validity guides, and were rejected. Most[46,48-50] were rejected on the basis of an ecological study design. Others[51-55] were rejected as a result of inadequately controlling for determinants of IMD status in the case and control group. In one study,[56] the case definition included asymptomatic carriage of *N. meningitidis* in the nasopharynx; this is not an indication of invasive disease, and thus the study was rejected. In the final study rejected,[57] risk factors reported had been subjected only to a one-tailed statistical test.

While of lower validity, the modifiable IMD risk factors reported in the rejected studies are summarized to illustrate similarity to those in identified in the key studies. Again, passive[54,55,57] and active[55] exposure to tobacco smoke was frequently cited as a risk factor in these studies. Crowded living conditions both in the general community[48] and in university residences[49,50] were identified as risk factors in ecological studies, as they were in the key studies. Socio-economic status was again identified as increasing IMD risk,[48, 57] as was antecedent upper respiratory tract infection.[53] Attendance at "discos" was identified as a risk factor in two small IMD clusters.[51,55] Several studies evaluated IMD risks associated with school-based activities,[46,52,56] although these studies would seem to assess the risk of being in close contact with a known IMD case. Working in a lab in which meningococcal bacteria are analyzed was cited as a risk factor in one ecological study.[47] While of a lower validity design, this exposure was evaluated in this research as a result of the significant descriptive epidemiologic evidence presented in the study, as is discussed in Section 3.8.2.

CHAPTER 3: METHODS

3.1 Study Objectives/Null Hypothesis

The primary objective of this research is to determine if modifiable risk factors for invasive meningococcal disease identified in high quality research are also risk factors among cases of invasive meningococcal disease identified in the Capital Health region (as the boundaries existed between April 1, 1998 and April 1, 2003) between December 1999 and June 2002. The null hypothesis is as follows: modifiable risk factors for invasive meningococcal disease reported in high quality studies the literature were not risk factors for invasive meningococcal disease cases in the Capital Health region between December 1999 and June 2002. A secondary objective of the study is to describe cases of invasive meningococcal disease identified during the outbreak.

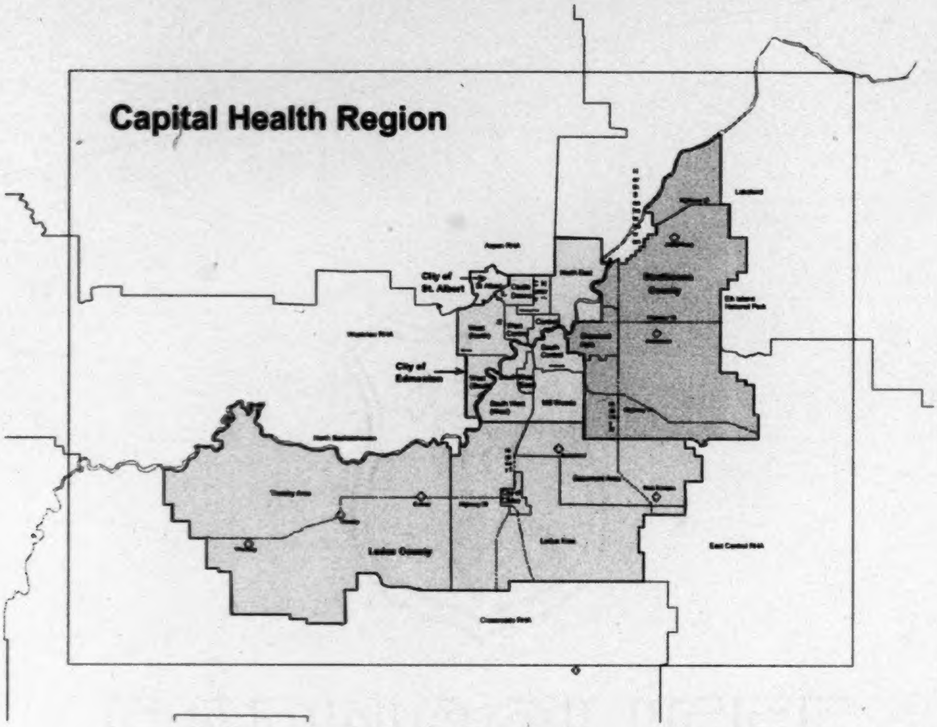
3.2 Study Setting

At the time of the outbreak, health care service delivery was regionalized in Alberta; the province was divided geographically into 17 Regional Health Authorities (RHAs) with each regional health authority being responsible for health care delivery within its boundaries. The setting for this population-based study was the Capital Health RHA, which included most of the metro Edmonton area. A map of this region with boundaries as they existed between 1998 and 2003 outbreak is seen in Figure 3.1 below. The mid-year population of the Capital Health region ranged between 819,120 (1999) and 859,409 (2002) during the outbreak.[58]

3.3 Study Design

A population-based matched case-control design was used. The relative rarity of IMD in the study population (the entire case series during the 31-month period of interest was approximately 80 cases) made case-control the design of choice. A retrospective design was necessary, as following the outbreak, IMD rates in the study population declined to historical baseline (approximately 1/100,000), making it likely that prohibitively few subjects would be available for a prospective study with reasonable statistical power. As will be discussed in more detail later, the reference (control) group was population-based and was recruited through random digit

Figure 3.1 Map of the Capital Health region, 1998-2003 boundaries*.



*Source: Population Health Division, Capital Health-Public Health Division. Reproduced with permission.

dialing; controls with the desired characteristics were more efficiently recruited in this manner than through other means (e.g. recruitment of hospital-based controls). Two controls were matched to each case to improve upon the precision of effect measures. Matching of three or four controls to each case, while further improving precision slightly, would likely have made this research cost prohibitive; as will be discussed later, controls were recruited on a per-unit cost-recovery basis.

3.4 Rationale for Matching

Matching was employed in the selection of controls, as a means of efficiently stratifying on two important potential confounders: age and sex. This allowed for equal distribution of age and sex across strata in the case and control group. Significantly different distributions of the factors among the study groups can result in zero or low cell counts when stratifying, resulting in a significant increase in the variance of measures of effect estimates, or, the loss of strata in the analysis.[59] Without matching, attaining a distribution of these factors that would allow for meaningful stratification would have necessitated the recruitment of significantly more study participants in the control group. Utilizing an unmatched design may have resulted in the study being cost-prohibitive or in the recruitment of a control group with age and sex distributions that would compromise the ability to stratify on these parameters. However, stratifying through the use of matching also introduces disadvantages, which will be discussed in the Limitations subsection of this report.

It is important to ensure that matching factors are true potential confounders for the disease of interest. It is well documented that both age and sex are correlated with important modifiable IMD risk factors in the population, including active smoking. In the 2001 Canadian Tobacco Use Monitoring Survey, it was reported that 22.5% of 15 to 19 year olds were smokers, compared with 32% in 20 to 24 year olds, and in the latter age cohort, smoking prevalence in males was 35% as compared to 29% in females.[60] The age-exposure association alone is not sufficient reason to select controls on these factors. If unrelated to IMD as well, matching on age and sex could result in a significant underestimation of the measure of effect.[59] As stated, there is significant evidence in the literature that both age and sex are important in the risk of IMD. Thus, stratification on these factors is necessary in estimating the importance of other risk factors.

3.5 Ethical Considerations

Prior to commencement of participant recruitment, application was made to the Health Research Ethics Board (HREB) serving the University of Alberta, Capital Health and the Caritas Health Group. On May 2, 2003, a meeting was held among Panel B of the HREB (the panel that reviews studies involving non-invasive health research), the primary researcher, and a member of the supervisory committee for the research (Dr. Stan Houston). Required revisions in recruitment procedures and scripts were provided by Panel B in correspondence dated May 16, 2003. The revisions were incorporated, and on June 3, 2003, HREB approval for this research was granted for a period of one year. Renewal of HREB approval was required when the study period exceeded one year, and on May 27, 2004, a one-year approval extension was granted. While not directly stated in the attached recruitment scripts, no remuneration was offered to study participants. Participants were provided with a telephone number of the office of the Medical Officer of Health for Capital Health as a means of obtaining additional information about IMD if desired, and the telephone number for the study supervisor as a contact for viewing the results of the research.

3.6 Sampling and Recruitment of Study Participants

3.6.1 Recruitment Process Summary

Both case and control group participants were recruited via telephone in a two-stage process. Eligible cases were contacted first by Capital Health, to elicit informed consent for contact by the researcher regarding study participation. The researcher then contacted cases that consented to being contacted, to elicit informed consent to participate in the study, which was followed by administration of the study questionnaire. Controls were contacted first by the Population Research Laboratory (PRL), Department of Sociology, University of Alberta, to elicit informed consent for contact by the researcher regarding the study among those meeting the eligibility criteria for the control group. The researcher then contacted eligible controls that consented to being contacted, to obtain informed consent to participate in the study, which was followed by administration of the study questionnaire. The entire recruitment process is described below.

3.6.2 Case Group Participant Recruitment

3.6.2.1 Case Definition

The case definition used in this study was laboratory-confirmed diagnosis of IMD in a resident of the Capital Health region, as per the April 1, 1998 and April 1, 2003 boundaries, reported to the Medical Officer of Health for the Capital Health region, with onset between December 1999 and June 2002 inclusive. The diagnostic criteria were:

- isolation of *N. meningitidis* from a normally sterile site (blood, CSF, joint, pleural or pericardial fluid), or
- demonstration of *N. meningitidis* antigen in blood or CSF, or
- positive *N. meningitidis* Polymerase Chain Reaction (PCR) test in blood or CSF

The above case definition was used by Capital Health during the IMD outbreak. It includes diagnostic criteria (demonstration of *N. meningitidis* antigen in blood, or positive PCR) not included in the most recent Health Canada definition,[61] which was revised during the outbreak. The Capital Health definition was retained, as diagnostic criteria omitted from the latest Health Canada definition were used in several key IMD risk factor studies, Health Canada is considering adding positive PCR test to the national case definition,[4] and antigen detection, while more sensitive in CSF, has been demonstrated in blood specimens.[62]

3.6.2.2 First Stage Recruitment Process, Case Group Participants

A telephone-based two-stage process was used for case recruitment. Representatives of the Office of the Medical Officer of Health for Capital Health were first to contact eligible cases (or proxies, as appropriate). If contact was successful, a standard recruitment script was read to the potential participant (see Appendix B). Informed consent was sought for both report of positive IMD status to the researcher and contact of the potential participant by the researcher regarding the study. This ensured that personal health information (IMD status) was provided to the researcher only after informed consent had been provided by the potential participant. Consent was provided over the telephone and recorded on an audio tape recorder.

Survivors 18 years of age or older at time of first-stage recruitment were contacted directly to participate in the study. Proxies for cases were sought to provide first-stage informed consent (and later, for participation in the study) in certain situations. A parent or guardian was sought for eligible survivor cases that were less than 18 years of age at the time of attempted contact. As discussed later, several IMD cases in the outbreak were fatal. It was decided that exposure information from these cases would contribute significantly to this research, and thus attempts were made to recruit a proxy study participant for each fatal case. For cases 18 years or older at the time of death, a parent, spouse or loved one was sought, and for fatal cases less than 18 years of age at death, a parent was sought.

Eligible cases were contacted by telephone, first using the telephone number for the case recorded in Capital Health's notifiable disease database. If this telephone number was out of service or had been reassigned, Capital Health staff sought the correct telephone number from another source. Health information databases consulted included the Alberta Health and Wellness Provincial Personal Health Identifier (PPHI) database (to which Capital Health personnel have access), and Capital Health's immunization database. Other databases consulted included an online telephone directory (http://www.mytelus.com/phonebook/index.vm), and an internet search engine (www.yahoo.com). If a database search yielded a telephone number different than appeared in the notifiable disease database, attempts were made to contact the potential participant at that number. Up to five attempts were made to contact potential participant at each telephone number found the potential case participant, during normal business hours, as well as on evenings and weekends. A standard message was left on answering machines at the telephone numbers contacted. If all telephone contact attempts were unsuccessful, a letter (Appendix C) regarding the study addressed to the case or proxy (as appropriate) was sent to the most recent address recorded in the health databases outlined above.

3.6.2.3 Second Stage Recruitment Process, Case Group Participants

Capital Health provided the primary researcher with the names and telephone numbers of cases (and proxies if appropriate) that provided first-stage informed consent. The researcher then attempted to contact each case/proxy by telephone for second-stage informed consent. It was during the second stage that the participant provided informed consent to take part in the study. The case or proxy that provided informed consent also provided consent at the second stage, with one exception: survivor cases 12 to 17 years of age at time of attempted recruitment. While a proxy provided first-stage consent, consent was required of both the proxy and the case at the second stage. As discussed later, a portion of the research questionnaire was administered directly to participants in this age cohort, necessitating their informed consent.

Upon successful contact of the potential participant, a standard script (Appendix D) was read to elicit second stage consent, and, as in the first stage, consent was recorded on audio tape over the telephone. Administration of the questionnaire commenced immediately after informed consent was obtained to participate in the study. Again, up to five attempts were made to contact potential participant at each telephone number found the potential case participant, during normal business hours, as well as on evenings and weekends. A standard message was left on answering machines at the telephone numbers contacted. If all telephone contact attempts were unsuccessful, a letter (Appendix E) regarding the study addressed to the case or proxy (as appropriate) was sent to the most recent address recorded in the health databases outlined above. If no response was received prior to May 1, 2004, the case was considered lost to follow-up.

3.6.2.4 Case Group Participant Recruitment Summary

A summary of first and second stage case recruitment appears in Table 3.1 below. First-stage recruitment of cases for the study took place between July 2003 and April 2004. Participants were recruited from among the 89 cases initially reported as being eligible by Capital Health. Two cases were deemed ineligible by Capital Health prior to first stage recruitment. One individual originally classified as a case was found not have met the case definition after a review of laboratory test results by Capital Health, and another that met the case definition was not contacted for participation at the request of Capital Health. A total of 51 of the 87 eligible cases were successfully contacted and provided first-stage consent. All but one of these cases was recruited between July and October 2003. Reasons for non-recruitment included refusal to participate after successful telephone contact, unable to locate correct telephone number for participant or unable to contact the participant by telephone after five attempts.

Second-stage recruitment for the case group took place between November 2003 and April 2004. Cases were deemed lost to follow-up if no reply to recruitment telephone calls or letters was received by May 1, 2004. A total of 44 cases of the 51 recruited at the first stage were successfully contacted and provided informed consent to participate in the study, who were then administered the study questionnaire. After review of IMD diagnostic information by the researcher, an additional four individuals originally classified as cases were found not to have met the case definition. Thus, the entire case series consisted of 84 cases, and the recruitment rate for the study was 52% (44/84). The denominator includes one case that met the case definition, but was not contacted for participation at the request of Capital Health. All of the 44 cases that were administered the study questionnaire met the case definition, and thus none of the data provided by these cases was excluded from the analysis based on review of case diagnostic information. Of the five individuals that were re-classified as non-cases, two were among the seven cases lost to follow-up between the first and second stage of recruitment, with the remainder from among those not successfully recruited at the first stage.

3.6.3 Control Group Participant Recruitment

As indicated, a population-based control group was used in this research. As for the case group, controls were recruited in two stages. The Population Research Laboratory (PRL),

Table 3.1 Summary of first and second stage recruitment for case group participants

First stage recruitment status (n=89)	Reason for non-recruitment*	Number of cases	Second stage recruitment status (n=51)	Reason for non-recruitment*	Number of cases
Recruited	Not applicable	51	Recruited	Not applicable	44
Unable to recruit	Change in telephone number after diagnosis, correct number not located	18	Unable to recruit	Change in telephone number after first stage recruitment, correct number not located	2
Unable to recruit	Unable to contact by telephone in five attempts	14	Unable to recruit	Unable to contact by telephone in five attempts	5
Unable to recruit	Refused to participate	4			
Recruitment not attempted	Deemed ineligible by Capital Health†	2			

*A recruitment letter was sent to all cases if unable to contact by telephone. Deemed lost to follow-up if no reply received by May 1, 2004

†Prior to first stage recruitment, one case was found not to have met the case definition, another that met the case definition was not contacted for participation at the request of Capital Health

Department of Sociology, University of Alberta, was contracted to assist with the first stage of control recruitment, both for reasons of practicality and the agency's experience in study participant recruitment of this nature. Three separate "waves" of first stage recruitment were required to obtain the desired number of controls. Potential participants were contacted from a pool of randomly generated telephone numbers. Those contacted were administered an eligibility questionnaire employing Computer Assisted Telephone Interviewing (CATI). If all eligibility requirements (including age and sex match to a recruited case) were met, the individual was asked for permission to be contacted by the primary researcher to discuss participation in the study. The primary researcher was provided pertinent information from the PRL on first-stage recruits, who then attempted to contact these potential participants for consent to participate in the study. The primary researcher met with PRL supervisory staff on several occasions to develop the control recruitment process, and with PRL telephone interviewers to assist with process-specific briefing and training, prior to commencement of each wave of control recruitment. The entire control recruitment process is elaborated upon below.

3.6.3.1 Eligibility Requirements for Control Group Participants

In case-control studies, it is important that controls, in addition to being free of the disease of interest at time of recruitment, are selected from the source population that gave rise to the cases, be at risk of the disease of interest when the case is diagnosed, and representative of the source population vis-à-vis the exposure.[63] These criteria were considered when formulating the control eligibility requirements for this study; namely, self-report of

- having never been ill with meningococcal meningitis nor meningococcemia, and
- having resided in the Edmonton area (operational definition for the Capital Health region) all the time since 1999 (i.e. during the entire outbreak period).

As indicated, controls were matched to cases by sex and age. The criteria for age matching varied on the age cohort. For cases that were greater than two years of age at onset, controls were matched to cases by exact age (in years) of the case on the approximate date of control recruitment. This approximate date varied depending on the first stage control recruitment wave during which the control was recruited. For controls recruited during the first wave, November 1, 2003 was the date used to calculate the age of the case, for the second and third waves, June 1, 2004. To account for possible differences in age-related immunity, different age matching criteria were used for cases less than two years of age at onset. Controls were matched to cases based on their age (to the ranges 0-6 months, 6-12 months or 12-24 months) as of the date of onset for the case.

3.6.3.2 Random-Digit Dialing Procedure for Control Group Participant Recruitment

The first step in the control group participant recruitment process was the random generation of telephone number samples. The methods used by the PRL in this regard are published elsewhere.[64] In Alberta, the local telephone service provider assigns customer telephone numbers (both listed and unlisted) in blocks corresponding to the first eight of the ten digits in a local telephone number (including a 3-digit area code prefix). These are made available to the PRL through a subsidiary of the local telephone service provider. A bank of 8-digit numbers corresponding to local telephone numbers assigned within the Capital Health region (1998-2003 boundaries) was prepared, from which a computer-generated random sample of these numbers was selected. The next step was to add randomly computer-generated two digit numbers (within the range 00 through 99) to the eight digit numbers already selected, to generate full ten digit telephone numbers. A sample of random numbers was generated for the first recruitment wave, and a new sample for the second and third wave. For each successive wave, telephone numbers included in the sample from the previous wave were excluded from being selected again.

3.6.3.3 Control Group Participant Study Eligibility Interview

The PRL prepared a report of the first stage recruitment interview telephone call procedure and data collection summary, which is found in Appendix F. PRL personnel carried out the telephone-administered interview at CATI facilities housed at the University of Alberta. The CATI software sequentially dialed the numbers from the random pool. If the telephone was manually answered at a residence (rather than a business), the PRL interviewer began administering the study eligibility questionnaire (also in Appendix F), which had been loaded onto computers at each interviewer call station.

The criteria for callbacks, number of callbacks per number and time of day of telephone calls[65] is summarized here. If a call was not manually answered for a particular telephone number, up to ten attempts were made for that number, on varying days (including weekends) and times of day (including evenings). Exceptions included the following: refusal to participate had been received, telephone line trouble, the number was not in service or a business/fax number, or the number had been cataloged as "Permanent No Contact" or "Family Crisis/Illness". For those numbers at which a language barrier had been encountered, PRL operators called at various times of day in an attempt to speak to someone else in the household that could communicate in English. "Permanent No Contact" refers to household members who were away during the recruitment period or would have been very difficult to reach for participation in the study (e.g. due to travel commitments). Some potential respondents also indicated that they would contact the PRL to verify the legitimacy of the study. A CATI supervisor contacted these households if a reply had not been received within one week.

Each telephone number had a 360-minute reattempt quota, meaning that interviewers did not dial the same number twice within a three-hour time cycle. This minimized the likelihood of a "no answer" or "answering machine" response. As well, at least one attempt was made to dial all eligible telephone numbers during evening hours, when the likelihood of contact is higher. CATI supervisors were also instructed to ensure that records were attempted or re-attempted at various times of day and evening. Some respondents provided a time at which they could be called back to discuss the study; interviewers called back at the time specified.

As for the case group, proxies (a parent or guardian) were administered the eligibility questionnaire when the control participant being sought was less than 18 years of age. Pertinent information regarding those who were administered the eligibility questionnaire (proxy and/or control, as appropriate), met eligibility requirements, and agreed to be contacted by the researcher, was entered into a database by PRL personnel. The database containing information regarding eligible first-stage proxies/controls was provided by PRL to the researcher either on a computer diskette or in a password-protected file sent via e-mail.

As discussed, first stage control group participant recruitment took place in three successive waves. Multiple first stage control participant recruitment waves were required to replace controls that refused to participate in the study after initial recruitment by the PRL or were lost to follow-up during second stage recruitment, and to recruit controls matched to a case that had been recruited after the first wave. The results of each first stage recruitment wave are summarized below.

3.6.3.4 First Stage Control Recruitment, First Wave

The first wave of first stage control recruitment took place in October and November of 2003. Two controls (matched on age and sex) were recruited for each of the 50 cases that had been recruited as of October 2003. A PRL operator was unsure if one recruited control met the recruitment criteria, and an additional control of the same age/sex was recruited as a precaution, making 101 the total number of controls recruited in the first wave. As is summarized in Appendix F, approximately 1.5% of the 6,571 total randomly generated telephone numbers for the first wave yielded recruitment of a control participant. A total of 13,963 telephone calls were needed to recruit these participants, or approximately two telephone calls per telephone number dialed.

There were several scenarios ("dialing dispositions") that resulted in a randomly generated telephone number not yielding a recruit during first wave. Approximately 35% of the random telephone numbers were not in service, or were assigned to a business or fax machine. Approximately 24% of all first wave telephone numbers reached a household with no residents of the required age, sex and/or length of residence in the Edmonton area. Approximately 12% of telephone numbers resulted in an "initial refusal to participate". In terms of number of CATI telephone calls required, approximately 25% of telephone numbers yielded no answer, a busy signal, an answering machine or instructions to call back later, which necessitated multiple call attempts.

3.6.3.5 First Stage Control Recruitment, Second and Third Waves

The second wave of first stage control recruitment took place in June of 2004, for which 26 controls were required. As discussed, seven of the 50 cases initially recruited had been lost to follow-up at the second stage. Thus, the 14 controls recruited for these cases during the first wave were not used in the final analysis, contributing to study inefficiency. Among the PRL recruited controls matched to the remaining 43 cases, 24 were lost to follow-up in the second stage of control recruitment by the researcher as discussed below. As indicated, one additional case was first and second stage recruited after the first PRL control recruitment wave, necessitating two additional controls, for a total of 26 controls needed in the second wave. A third wave of recruitment took place in July 2004. This additional wave was required, as three of the 26 controls recruited in the second wave were lost to follow-up at the second stage.

A summary of second and third wave CATI call attempts (Appendix F), which resulted in the recruitment of 29 (26+3) total participants, was similar to that of the first wave. Approximately 1% of the 3,811 total randomly generated telephone numbers for the first wave yielded recruitment of a control participant. A total of 6,587 telephone calls were needed to recruit these participants, or approximately two telephone calls per telephone number dialed. As in the first wave, there were several scenarios that resulted in a randomly generated telephone number not yielding a recruit. Again, approximately 35% of the random telephone numbers were not in service, or were assigned to a business or fax machine. Approximately 27% of all first wave telephone numbers reached a household with no residents of the required age, sex and/or length of residence in the Edmonton area. Approximately 8% of telephone numbers resulted in an "initial refusal to participate". In terms of number of CATI telephone calls required, approximately 25% of telephone numbers yielded no answer, a busy signal, an answering machine or instructions to call back later, which necessitated multiple call attempts.

3.6.3.6 First Stage Control Recruitment Efficiency

Summary measures of random digit dialing efficiency described elsewhere[75,76] were calculated, and are presented in Table 3.2 below. Only about half of all generated numbers reached households. Rather than random error, this is likely a measure of the household/non-household ratio for telephone numbers provided to the PRL by the local telephone company subsidiary. Response rates among households successfully contacted are comparable to that observed in other telephone-administered questionnaires facilitated through random-digit dialing.[76] The recruitment rate is a reflection of the stringent recruitment criteria in this study. A lower recruitment rate was anticipated and observed in the second and third waves as compared to the first wave, a result of the reduction in the probability that those contacted would meet the eligibility criteria for the remaining control participants required.

Table 3.2 Recruitment efficiency rates for first stage control recruitment

Control recruitment efficiency rate	**Recruitment wave**		
	1st wave	**2nd and 3rd waves**	**Aggregate**
Sampling efficiency[a]	3,478/6,571=52.9%	2,006/3,811=52.6%	52.8%
Completion rate[b]	1,690/3,478=48.6%	1,084/2,006=54.0%	50.6%
Cooperation rate[c]	1,690/1,690+765=68.8%	1,084/1,084+298=78%	72.3%
Recruitment rate[d]	100/1,690=5.9%	29/1,084=2.7%	4.7%

[a] Number of telephone numbers dialed that reached a household/total number of randomly generated telephone numbers dialed
[b] Number of households administered the eligibility questionnaire/total number of households dialed
[c] Number of households administered the eligibility questionnaire/total number of households at which telephone was answered (i.e. number administered questionnaire + initial refusals)
[d] Number of eligible controls recruited/total number of households administered the eligibility questionnaire

3.6.3.7 Cost of First Stage Control Recruitment

Cost recovery by the PRL for first stage control recruitment was a significant expenditure for this research. The total and unit cost charged by the PRL for control recruitment is summarized in

Table 3.3 below. A total of 129 controls were recruited by the PRL for the study. Only 88 were used in the study (for the reasons described above), for an efficiency of approximately 68%. The average unit cost for first stage recruitment of controls was $133.29, however, the unit cost for recruitment of the 88 controls actually used in the study was $160.60. The unit cost differed for each recruitment wave, based on increased operating costs at the time each subsequent recruitment wave was initiated. As well, administrative costs charged for the first and second wave did not vary based on the number of controls required, resulting in a significantly higher unit cost in the second wave (administrative costs were not charged for the third recruitment wave). The PRL significantly underestimated the number of telephone calls (and thus the cost) that would be required to recruit cases for the first wave; the actual cost was approximately 40% higher than the initial estimate provided to the researcher. However, a discount of approximately 20% was provided due to the large discrepancy in the quoted versus the actual cost. The discounted rate is used for the purposes of cost calculations.

Table 3.3 Total and unit cost of first stage control recruitment by the PRL ($CDN)

Recruitment wave	Total Cost	Unit Cost
First*	7,917.10	79.17
Second	5,938.77	228.41
Third	276.90	92.30
Total	14,132.77	n/a
Mean	n/a	133.29

*A discounted rate is shown. The actual total cost/unit cost was $9,699.10/$96.99

3.6.3.8 Second Stage Recruitment Process, Control Group Participants

The researcher contacted potential control participants provided by the PRL by telephone, in a similar manner to second stage recruitment of cases. Again, it was during the second stage that the participant provided informed consent to take part in the study. The control or proxy that provided informed consent also provided consent at the second stage, with one exception: survivor cases 12 to 17 years of age at time of attempted recruitment. While a proxy provided first-stage consent, consent was required of both the proxy and the control at the second stage. As discussed later, a portion of the research questionnaire was administered directly to participants in this age cohort, necessitating their informed consent.

Upon successful contact of the potential control group participant by the researcher, a standard script (Appendix D) was read to elicit this consent, and, as in the first stage, consent was recorded on audio tape over the telephone. As for cases, administration of the study questionnaire commenced immediately after informed consent was obtained to participate in the study. Again, up to five attempts were made to contact potential participant, during normal business hours, as well as on evenings and weekends. A standard message was left on answering machines at the telephone numbers contacted. If all telephone contact attempts were unsuccessful, the participant was recorded as being lost to follow-up. The PRL was then asked to seek another participant with appropriate eligibility requirements in a subsequent recruitment wave.

3.6.3.9 Control Group Participant Second Stage Recruitment Summary

Second-stage recruitment for the control group took place between March and July of 2004. Controls recruited by the PRL in the first wave were contacted between March and May 2004. After accounting for seven of 50 initial cases lost to follow-up, 86 (43 x 2) controls were required. Of these 86 controls, 24 were lost to follow-up. That is, the participant that initially consented to being contacted about the study refused to participate further when contacted by the researcher, the telephone number provided to the PRL for the control participant was incorrect/out of service, there was continually no answer at the telephone number provided after five attempts, or, messages left at the telephone number provided were not returned after five call attempts. Similarly, controls recruited by the PRL in the second wave were contacted in June and July 2004. This included 26 controls: the 24 lost to follow-up at the second stage, and two additional controls for a case recruited in April of 2004. Of these 26 controls, three were lost to follow-up. These final controls were both recruited by the PRL and successfully contacted by the researcher for second stage consent in July of 2004. Through these efforts, the complete control set of 88 was recruited and administered the instrument. Second stage control recruitment is summarized in Table 3.4 below.

3.6.4 Timing of Invasive Meningococcal Disease Onset, Recruitment and Questionnaire Administration

Significant periods of time elapsed between case IMD onset and first stage recruitment, and between the first and second stages of recruitment/questionnaire administration, as summarized in

Table 3.4 Summary of second stage recruitment for control group participants

Second stage recruitment status, wave one controls (n=100)*	Reason for non-recruitment	Number of controls	Second stage recruitment status, wave two controls (n=26)†	Reason for non-recruitment	Number of controls
Recruited	Not applicable	62	Recruited	Not applicable	23
Unable to recruit	Unable to contact by telephone in five attempts	14	Unable to recruit	Unable to contact by telephone in five attempts	3‡
Unable to recruit	Change in telephone number after first stage recruitment (by PRL), correct number not located	6			
Unable to recruit	Refused to participate	4			
Recruitment not attempted	Matched case lost to follow-up	14			

*two per case recruited (50) as of start of first stage, wave one control recruitment

†number of controls required for first stage, wave two recruitment was the sum of the number of controls from first stage, wave one recruitment for which the researcher was "unable to recruit" at second stage (24), plus two controls for a case that was recruited after wave one control recruitment

‡the three controls lost to follow-up from first stage, wave two control recruitment were first stage recruited in a third wave; all were successfully second stage recruited. Thus, the total number of controls recruited in the second stage was 88 (62+23+3), or two per the 44 cases second stage recruited cases

Table 3.5 below. On average, study participants were asked to recall exposures during a one-month period approximately three years in the past. Approximately 2.5 years had elapsed between the start of the IMD outbreak and the time at which the study was first conceived, which would account for much of the delay between case onset and start of first stage case participant recruitment. An additional year was required for research proposal development and ethics approval. Delays between first stage recruitment and second stage recruitment/questionnaire

Table 3.5 Elapsed time intervals between IMD onset, first stage recruitment, and second stage recruitment/questionnaire administration (cases and controls aggregated)

Time interval Description	Time interval, days (years)				Difference in means (p-value)[a]
	Cases		Controls		
	Range	Mean	Range	Mean	
Date of IMD onset to date of first stage recruitment[b]	410, 1,378 (1.12, 3.78)	937 (2.57)	n/a	n/a	n/a
Date of first stage recruitment to date of questionnaire administration[c]	1, 254 (0.002, 0.70)	188 (0.52)	1, 204 (0.002, 0.56)	123 (0.34)	<0.001
Date of IMD onset to date of questionnaire administration[d]	522, 1,526 (1.43, 4.18)	1,125 (3.08)	708, 1,636 (1.94, 4.48)	1,231 (3.37)	0.046

[a] t-test for equality of means
[b] cases only; this time interval not of relevance for controls
[c] date of questionnaire administration was the same date as second stage recruitment
[d] for controls, the date of onset used was the first day of the first month of the month and year of onset for the control's matched case

administration were a result of task prioritization by the researcher, who was employed full time while conducting this research. Following first stage case recruitment, the researcher focused on first stage recruitment of controls. Following the first wave of first stage of control recruitment, the researcher focused on second stage recruitment of cases, resulting in a delay in second stage recruitment of controls. Significantly different time intervals elapsed for cases and controls between first stage recruitment and questionnaire administration, which has implications for recruitment efficiency, and between exposure period of interest and the date of questionnaire administration, which has implications vis-à-vis recall bias.

3.7 Statistical Power

The statistical power for the study was calculated as per published methods.[77] Several calculations were required, as several exposures were measured only in specific age cohorts. The maximum detectable odds ratios below 1.0 (protective associations were anticipated) and minimum detectable odds ratios above 1.0 were calculated for each age cohort, summarized in Table 3.6 below. An α level of 0.05 and a β of 0.2 (i.e. power of 0.8) was assumed, along with

Table 3.6 Maximum protective, minimum risk factor odds ratios detectable for study participant age cohorts in which exposures were measured, with $\alpha=0.05$, $\beta=0.2$ and 20% exposure rate assumed in the study population

Age cohort (years)	Number of cases, controls in age cohort	Maximum odds ratio detectable below 1.0	Minimum odds ratio detectable above 1.0
<5	8, 16	0.000	13.37
<18	17, 34	0.009	5.847
≥12	33, 66	0.111	3.647
≥16	31, 62	0.098	3.788
All ages	44, 88	0.173	3.105

an exposure rate of 20% in the study population. A 20% exposure rate in controls is higher than the 15% used in a similar study;[34] however, it is reported in the 2000/01 Canadian Community Health Survey that 23% of survey respondents in the Capital Health region were daily smokers.[78] As smoking is arguably the most important IMD modifiable risk factor, an exposure rate of 20% in the control group was seen as a reasonable compromise for the purposes of this study.

3.8 Data Collected from Participants

3.8.1 Exposure Period of Interest

As indicated, infection with *Neisseria meningitidis* typically occurs within ten days of exposure to the pathogen. The narrow exposure period for IMD presents a challenge in retrospectively measuring exposures among study participants, in that recall of events during ten-day window that occurred more than one year previously is not intuitively appealing. This is especially true for those in the control group, who lack a "recall stimulus"[66] equivalent to case participants. For this reason, the exposure period of interest in this study was the month before illness onset in case participants, and for controls, the calendar month of illness onset for the case to which each control was matched. A one-month exposure window has also been used in several of the key IMD risk factor studies reviewed above.[31,38,39,41,43,45]

3.8.2 Invasive Meningococcal Disease Risk Factor Information

A summary of risk factor categories for which information was collected from participants is found in Table 3.7. A total of 67 risk factors were measured. Modifiable factors were included

Table 3.7 IMD risk factor information collected from participants, by age cohort (*denotes risk factor measured only among cases)

Age cohort (at onset, years)	Risk factors measured
All ages	• Residence in Canada • Intra/international travel • Oral muscle tone (snoring, speech pathology) • Household population density (number of bedrooms, number of residents, number residents <10 years of age) • Sharing of bedroom • Household heating type • Household humidifier usage • Household particulates (wood fireplace, household renovation dust) • Respiratory infection (fever and cough)* • IMD immunization status • Predisposing health conditions • Contact with IMD case • Household income • Passive exposure to environmental tobacco smoke - within household (number, category of household resident smokers) - outside household (frequency of visits to indoor environments outside of home where others smoking) • Sharing of drinks/utensils/toothbrushes/lipstick* • Lips kissing/number of lip-kissing contacts • Exposure to crowded public places (public transit usage, church attendance, team sports/organized physical activity) • Aboriginal status
<5 years	• Breastfeeding (ever breastfed, age stopped) • Maternal prenatal smoking • Daycare/preschool/day home/organized play group attendance
<18 years	• Maternal education

≥12 years	• Active smoking (including frequency/dosage if applicable) • "Rave"/party/gathering attendance
≥16 years	• Bar/night club attendance • Residence in college/university dormitories • Employment in laboratory where meningococcal bacteria analyzed • Life events/stress

in the instrument if they were cited in the key modifiable risk factor studies reviewed or if there was significant evidence indicating that the factor may increase IMD risk (discussed below). Non-modifiable risk factors were included if cited in medical research as an IMD risk factor, or if the factor is known to significantly impact general health status (such as aboriginal status).[94] Age-correlated exposures were measured only for participants in appropriate age categories. For example, information regarding active smoking was collected from participants 12 years of age or older at IMD onset. Measurement of smoking in this age cohort reflects findings in a large Canadian study (National Longitudinal Survey of Children and Youth), in which it was reported that the number of ten and 11 year olds smoking was "too few to report", while the smoking prevalence in this same group at age 12 and 13 was 10%.[67] Some questions were asked only of those 16 years of age and older (i.e. information on patronage in bars, attendance at college or university classes, etc.). Information on breastfeeding and daycare attendance was sought in participants less than five years of age at onset.

Information was collected regarding attendance at "raves", which have been defined as all-night youth oriented electronic music dance events held in makeshift dance halls.[68] Two IMD cases in the outbreak were thought to have attended the same "rave-like event",[69] and thus, this exposure was included in the questionnaire. Questions regarding rave attendance were asked of participants 12 years of age and older, as alcohol may not be served at such events, meaning that those under the age of 18 may have been permitted to attend.

Operational definitions were formulated for exposures such as crowding and upper respiratory tract infection. Household density was calculated as the ratio of residents living in the participant's household to the number of bedrooms in the household, with number of residents less than ten years of age multiplied by a factor of 0.5. This household density calculation method was used as a measure of household crowding in a key IMD study.[39] Illness with fever and cough was used as a proxy measure of upper respiratory tract infection; fever and cough together constitute a clinical case definition for URTIs that are important vis-à-vis IMD risk, such as influenza.[70]

Information was collected regarding some IMD risk factors not of significance in the key studies reviewed. However, significant descriptive epidemiologic evidence warranted controlling for additional IMD risk factors in the analysis. These included specific health conditions (asplenia,[26] complement deficiency)[27] and employment in laboratories where meningococcal bacteria are analyzed.[47] HIV status was included, as a result of the observed association between HIV infection and bacterial infections, especially those of the upper respiratory tract.[98] History of cancer, diabetes or kidney disease requiring dialysis was also included to as a result the association between compromised immunity and these conditions.

3.8.3 Invasive Meningococcal Disease Immunization Status

The IMD immunization status of study participants was an important consideration in this study. As indicated, early in the outbreak an IMD immunization program for high-risk age groups (two to 24 years of age) was initiated early in the outbreak (February 2000) in the Capital Health region. In September 2001 Capital Health residents two to 23 months of age were also eligible to receive a newly licensed vaccine effective for this age group. It is also recommended that those travelling to an area where IMD is endemic are immunized.[71] Thus, all study participants were asked if they had ever received the meningococcal meningitis "shot". However, two additional pieces of information were considered when assessing the vaccine-mediated IMD immunity status of a case or matched control: timing of IMD immunization in relation to onset, and the serogroup with which the case had been infected. Participants that had both received the immunization prior to onset (or prior to the month of onset of matched case, for controls) and had been infected with an IMD serogroup for which vaccines administered provide immunity (i.e. A, C, W-135 or Y) were classified as having IMD vaccine-mediated immunity. If a control's matched case was known to have been infected with serogroup B, both the control and the case were classified as non-immune, even immunization had been received prior to case onset.

If it was reported that the participant had not received IMD immunization and was eligible to receive the vaccine during the immunization campaign undertaken in Capital Health, the participant/proxy was asked a question regarding reason(s) for not being immunized. Those eligible for immunization included participants that were aged two to 24 years of age at any time during the campaign, i.e. between February 2000 and March 2002. Participants that had onset of IMD prior to the start of the immunization campaign were deemed as being ineligible for the vaccine.

3.8.4 Change in Invasive Meningococcal Disease Risk Behaviors

Participants were asked questions regarding changes in behaviors that are known IMD risk factors, following the month of interest i.e. for cases, after IMD onset, and for controls, after the calendar month of onset for the matched case. These questions were asked regarding changes in passive exposure to tobacco smoke (all ages), active smoking (participants ≥12 years of age), and attendance at bars or other establishments where alcoholic drinks are served (participants ≥16 years). Change in these risk behaviors were assessed through polychotomous closed-ended questions in which it was asked if the participant had more, less or the same amount of the exposure at the time of questionnaire administration, as compared to the month of onset.

3.8.5 Request for Participation in Another Invasive Meningococcal Disease Study, Case Group Participants

During the study period, Capital Health was approached by a research group at the University of Sherbrooke (Quebec, Canada) conducting a nation-wide IMD study. Data for the study were to be collected from confirmed IMD cases via a self-administered mail-in questionnaire. At Capital Health's request, case group participants were told about the study following administration of the questionnaire, and were asked if they would be willing to provide a mailing address to which the questionnaire for the Quebec study could be mailed. Following collection of data from all case group participants, and prior to this mail-out, Capital Health was advised that the Quebec IMD research study had been discontinued. A letter (Appendix G) was mailed to study participants that had provided a mailing address, to advise that their participation in the Quebec study would no longer be required.

3.9 Data Collection Instrument

Study data were collected using an interviewer (telephone) administered questionnaire, which is found in Appendix H. No validated questionnaire suited for this research was available, which presented a threat to validity and reliability. However, the instrument was adapted from questionnaires used in key IMD risk factor studies reviewed above.[31,34,40] At the request of the researcher, electronic versions of the instruments used in these studies were provided via e-mail by corresponding authors. A complete instrument was prepared, containing all exposures of interest. The nature of the study precluded blinding of the researcher to case/control status. While this presented a threat to study validity, it was anticipated that interviewer bias was minimized through the use of a standard instrument crafted to elicit closed-ended dichotomous responses. This research presented several challenges vis-à-vis questionnaire measurement of potential risk factors, including age-dependent risk factors in a study group with a wide age distribution, significant time lapse between the exposure period of interest and questionnaire administration, sensitive nature of some questions and measurement of exposures for fatal cases. These challenges were taken into account in the design of the study instrument.

Most exposures were assessed using dichotomous (yes/no) responses. Continuous variables were used for number of years in Canada prior to onset, household density measures (number of residents, number of bedrooms, calculated density value, number sharing bedroom), age at which breast feeding was stopped, number of household smokers, number of cigarettes smoked daily (active smokers) and number of lip-kissing contacts. Polychotomous categorical responses were used in measuring maternal education, household income, stress level, reason for not being immunized and change in IMD risk behavior after month of interest. For all questions, "don't know", "not sure" and "refused" response categories were also included.

Several strategies were employed in the collection of information from various participant age cohorts. Branching on age of participant at onset was used in the instrument to facilitate collection of age-dependent exposure information appropriate to the participant. In addition, wording of the questions was modified for administration to proxy respondents as appropriate. For example, "Did you travel outside of Canada during 2000" was the question posed to survivors/matched controls 18 years of age or older, "Did your child travel ..." was asked of a parent of a survivor/matched controls less than 18. As indicated, some questions were asked directly of those 12 to 17 years of age at the time of questionnaire administration. To facilitate privacy of responses for these participants, parents were asked in the instrument script (Appendix H) to go to a place where they could not hear the answers their child provided for that part of the questionnaire administered directly to their child. The Flesch-Kincaid grade level of the instrument (as measured by Microsoft Word 97®) was maintained below 5.0 in that portion of the questionnaire administered directly to 12 to 17 year olds, and below 8.0 overall, to facilitate clear understanding of survey questions.

Question order was considered in the development of the instrument. Several questions in the questionnaire were of a sensitive nature, such as those regarding smoking, attendance at bars, and emotional stress. Sensitive questions were generally asked later in the interview, with less invasive questions such as those regarding the participant's dwelling and travel history asked first. As discussed below, questions regarding general categories of exposure such as household density and smoking were clustered, with questions flowing from general to specific.

As was discussed in the Section 3.6.4, a significant period of time had elapsed between the one-month exposure period of interest, and the administration of the questionnaire. In some cases, participants were asked to report exposures that took place as long as 4.5 years prior. To assist in participant recall, "bounded recall", "cueing" and a general-to-specific question order were used, each of which are strategies recommended elsewhere in this regard,[72] were used. For example, "Have you ever smoked at least one cigarette", "Has there ever been a time in your life that you smoked cigarettes more than once on a month", "would you say that [month, year of interest] was a time in your life that you smoked cigarettes more than once in a month" was the series of questions used to assess smoking status. The series of questions was preceded by the statement "I'm now going to ask you some questions about smoking". This along with multiple questions on an exposure cued participant recall, as the reference period of interest narrowed to the particular month of interest.

3.9.1 Pre-testing of the Instrument

The instrument and recruitment scripts were pre-tested to assess individual question meaning and task difficulty, as well as the flow, order, branching, timing and the fatigue and well-being of participants in the instrument as a whole, as is recommended elsewhere.[72] IMD cases and non-cases in various age cohorts participated in the pre-testing. To conserve statistical power, pre-testing case participants were not selected from the study population. Rather, confirmed IMD cases (as per case definition above) that occurred during the outbreak period and resided at an address outside of the Capital Health region prior to April 1, 2003, but within the expanded boundaries of the Capital Health region after that date, were selected. Five cases were eligible to participate in the pre-testing based on these criteria, and were recruited in the same manner as for study participants (described above), three of whom were successfully contacted and agreed to participate.

Twenty-three pre-tests of the instrument took place, among three cases and 20 non-cases. The age distribution of the cases (all of whom were young adults) was beyond the researcher's control. However, non-case participants of varying age were administered the questionnaire in the pre-testing phase. Proxies (parents) for individuals less than five years of age, five to 11 years of age, and 12 to 17 years of age during the outbreak period participated. Inclusion of the latter cohort allowed for pre-testing of questions in the instrument administered directly to children 12 to 17 years of age. The instrument was also pre-tested with young adults (i.e. 18 to 24 years of age) and middle aged and senior adults (30 to 60 and >60 years of age).

Pre-testing resulted in refinements of individual questions. For example, task difficulty issues were identified for the series of questions regarding categories of individuals that resided with the participant that smoked during the month of interest. Residency of certain categories of individuals in the participant's home and the smoking status of these individuals during the month of interest was initially combined in one question. Pre-testing participants seemed to have difficulty in combining the two concepts as presented verbally. Thus, in the final version of the instrument, the question was subdivided, e.g. "did your mother reside with you during [month of interest]?", [if yes] was she a smoker at that time?".

Recall of certain exposures by non-case pre-test participants was poor. Specifically, questions regarding illness with a fever and/or cough and sharing of drinks, utensils, toothbrush or lipstick/lip balm during the month of interest generally elicited a "don't know/not sure" response. Pre-test cases had better recall of these exposures, perhaps a result of the "recall stimulus"[66] provided by their illness with IMD immediately after the month of interest. These questions were asked only of cases in the final version of the questionnaire, due to the importance of these exposures as potential IMD risk factors, and the demonstrated recall of these exposures by cases during the pre-test.

No other major revisions were required for instrument (nor recruitment script) length, branching, flow and order, and few wording changes required for individual questions. An average of approximately 20 minutes was required to complete the questionnaire (including second-stage informed consent script) which did not seem to elicit fatigue in respondents. Well-being of IMD cases did not appear to be compromised in recalling events just prior to a traumatic time in their life; there were no response refusals (including sensitive questions), or requests to halt the interview. There were generally few "don't know/not sure" responses given to questions seeking recall to specific one-month periods, which was important in the context of this study. After pre-testing, a final version of the instrument was crafted and used for the study proper.

3.9.2 Administration of Questionnaire to Study Participants

As indicated, the researcher telephone-administered the questionnaire to both cases and controls immediately after second stage informed consent had been by the participant. Responses provided by each participant were recorded by the researcher on a hard copy of the instrument during the interview. Each completed questionnaire was given a letter-number code, corresponding to case/control status and participant number. On completion, the informed consent script (which included name and telephone number of the participant, and proxy if appropriate) was detached from the questionnaire.

3.10 Data Collection for Case Series Descriptive Analysis

To facilitate descriptive analysis of the entire outbreak case series and comparison of recruited and non-recruited cases, Capital Health provided the researcher with information on certain characteristics of all IMD cases reported during the outbreak. This information included sex, date of onset, age at onset, IMD serogroup (and genetic clone within the predominant serogroup), laboratory methods used for diagnosis, IMD immunization status at onset, clinical presentation (meningitis or meningococcemia) and if case was fatal. Personal identifiers were removed from these data to preserve ethical integrity.

3.11 Data Coding, Entry and Cleaning

Information on hard copies of the questionnaire (and case series data collection sheet) was coded to facilitate data entry. Most questions in the instrument required minimal coding prior to data entry, as answers elicited were frequently dichotomous in nature; "yes", "no" as well as "don't know", "not sure" and "refused" responses were given numerical codes. Presence/absence of vaccine-mediated immunity prior to onset was coded as per criteria outlined earlier. Computations involving continuous variables were required in some situations to derive values meaningful for the analysis. For example, information on number of residents and bedrooms in the household was used to calculate a value for household density (as described earlier). The number of cigarettes smoked daily, if reported in terms of cigarette packs, was multiplied by 20 cigarettes/pack to derive a value in terms of number of cigarettes. Number of years resided in Canada prior to onset was calculated by subtracting years since case onset from total number of years residing in Canada.

Information collected on study questionnaires was double entered into a spreadsheet software application (Microsoft® Excel 97). All data entry was carried out by one individual (the researcher). The computer files were imported into a statistical application (SPSS© 12.0 for Windows) for data cleaning. Frequencies of responses for all variables on the instrument were compared between the two entered datasets, and all inconsistencies identified were manually examined on the questionnaire hard copies to determine the correct value. Non-permissible values were also monitored for and corrected as appropriate. A complete, verified dataset resulted from these activities, which was used in the analysis.

3.12 Data Analysis

Data pertaining to the full IMD outbreak case series (provided by Capital Health), case and control recruitment, and all information collected in the study instrument were first subjected to descriptive analysis. A comparison of the recruited and non-recruited cases on the parameters provided by Capital Health was made, including an assessment of statistically significant differences in the two groups, using the Pearson χ^2 test (categorical variables) or t-test for equality of means (continuous variables) as appropriate. Descriptive analysis of questionnaire responses allowed for an assessment of unknown or missing questionnaire responses, exclusion of some variables from the univariate analysis, and for a description of variables that were collected only from the case group. Frequencies were used in describing dichotomous and polychotmous categorical variables, and measures of central tendency for continuous variables.

Conditional logistic regression (as per published methods[73] described below, with SPSS© 12.0 for Windows) was used in testing associations between exposures and development of IMD. Two regression analyses were conducted, one including the entire study data set, and one including data only from cases, and a sub-analysis including only cases with the predominant IMD serogroup/genetic clone (and their matched controls). The sub-analysis was carried out to compare risk factors for cases with the "outbreak" serogroup to those for all IMD cases. Some variables were transformed or re-coded to facilitate this analysis. Participants were classified as being non-exposed in the regression analysis if the information was missing, participant refused to provide information on the exposure, answered "don't know" or "not sure" in relation to that exposure, or if the participant was of an age that precluded collection of information regarding the exposure. For two exposures (frequency of passive exposure to cigarette smoke outside the home, and frequency of active smoking), separate variables corresponding to light versus no exposure and heavy versus light exposure were merged into one trichotomous variable. Heavy and light exposure was then assessed together, with no exposure as the reference group. Matched odds ratios were calculated as the risk estimate (e^{β} from the logistic model). Each exposure association was first subjected to univariate analysis. The significance of point estimates (95% confidence interval and p-value) was assessed utilizing a comparison of the Wald statistic χ^2 test.

"Purposeful" selection methods were employed in building the multivariate model; that is, the researcher assessed which variables should be included in the model at each step.[74] Challenges were encountered in multivariate analysis as a result of low cell counts and concomitant instability exhibited by several exposure-disease relationships. Variables exhibiting "complete separation" (i.e. those without a discordant pairs in either the numerator or the denominator of the Mantel-Haenszel matched odds ratio expression) were highly unstable (i.e. standard error values over 100 and confidence interval upper limits several orders of magnitude above 100). Variables exhibiting complete separation were not included in the model building process. Remaining variables with a p-value of less than 0.25 (likelihood ratio χ^2 test with k-1 degrees of freedom, where k is the number of levels of the exposure) were first selected as candidates for the multivariate model. An exception was vaccine-mediated IMD immunity, which had a likelihood ratio p-value of >0.25, but was forced into the model due to its clinical importance for IMD risk.

Unstable variables in this model were removed one at a time in order to detect colinearity among removed variables; if the removal of one variable resulted in stability among other variables, the removed variable was kept out of the model. Polychotomous variables with an unstable category were collapsed into a dichotomous variable. Remaining variables fitted in this first model that achieved statistical significance ($p<0.05$, Wald statistic) were fitted in a reduced model. When none of the variables in this model achieved statistical significance, multivariate analysis was carried out which included unstable variables in the first model.

Again, variables with likelihood p-values below 0.25 were included in the first model in the second model-building strategy, and variables fitted in this first model that achieved statistical significance ($p<0.05$, Wald statistic) were fitted in a reduced model. The significance of all variables removed from the first model was assessed with the likelihood ratio test, comparing the first model with the reduced model. Variables in the reduced model still exhibiting unstable properties, or that had a Wald statistic of $p>0.05$, were removed from the model. A test for statistical confounding was then carried out. Removed variables were added back one at a time; if the β coefficient of any of the variables in the model changed by more than 15% upon addition of a removed variable, the removed variable was re-introduced into the model.

Tests were conducted for linearity of continuous variables and for plausible interactions in the model. The β coefficients for continuous variables in the logistic model are assumed to be linear. This assumption was checked by determining if a plot of β coefficients for continuous variables in the model versus variable mid-quartile points was linear. Plausible interactions among variables in the resultant model (the "main effects model") were then added one at a time. Those exhibiting statistical significance (Wald test $p<0.05$) were kept in the model.

3.13 Methods Summary and Control of Potential Biases

The methods presented outline a population-based case-control study assessing modifiable risk factors in IMD cases. Several threats to validity are inherent in this study design, including recruitment bias, interviewer bias, measurement bias, non-response bias and bias introduced by differences in known and unknown determinants of outcome (i.e. IMD status) in the case and control groups, respectively. Multiple strategies were employed in minimizing bias in this research. Recruitment of the case group, which included all eligible individuals within the study population, was vigorous. The reference group was systematically and randomly selected from the source population for the case group. The questionnaire was modified from those used in similar studies, pre-tested to maximize face, content and criterion validity, and was administered to all study participants by the same individual. Known risk factors were controlled for by matching (age and sex) or were measured in the instrument and included in multivariate analysis. Limitations remain despite these strategies, and will be discussed later in this report.

CHAPTER 4: RESULTS

4.1 Eligibility for Inclusion in Case Series

Capital Health initially reported that 89 patients met the case IMD definition. After review of information provided by Capital Health regarding these cases, five lacked laboratory diagnostic test results as outlined the case definition, and therefore were excluded from the case group. These excluded cases may have been initially classified as such by Capital Health to achieve surveillance of maximum sensitivity during the outbreak (at the cost of specificity), for preventing disease transmission to contacts of suspected IMD cases. Unfortunately, as will be discussed, this resulted in some study inefficiency, as resources were initially expended to recruit cases and controls based on the information initially reported by Capital Health. However, to minimize classification bias in this research, only the 84 cases that met Capital Health's stated case definition were included in the study population. A description of this case series follows.

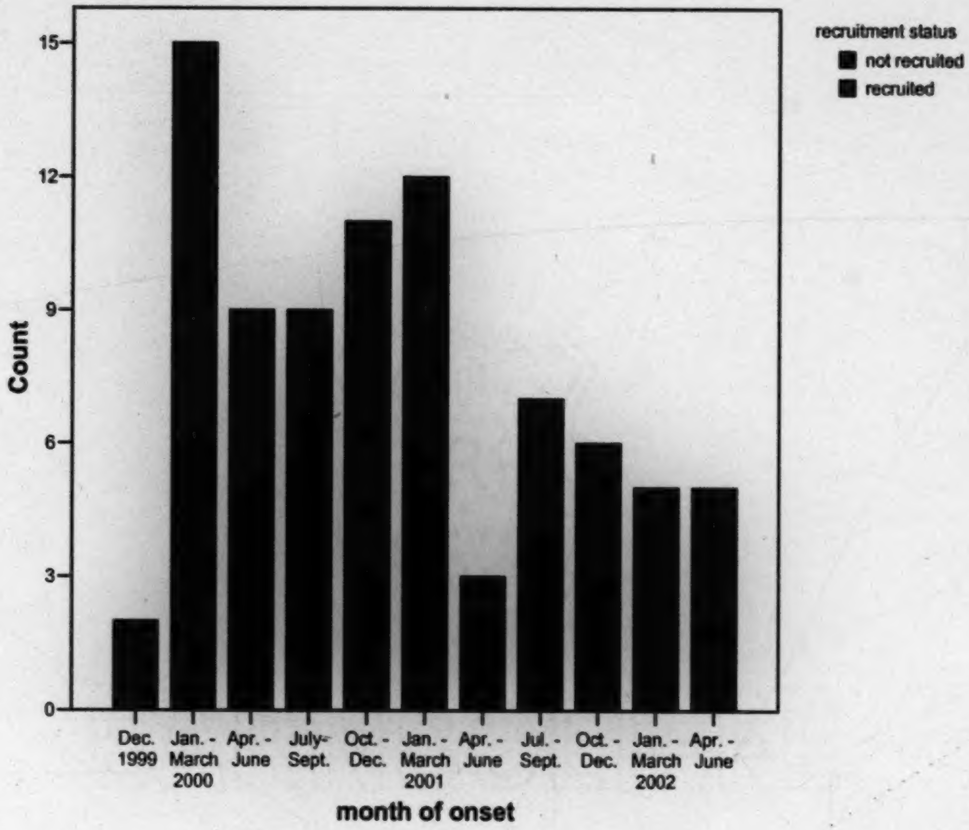
4.2 Invasive Meningococcal Disease Case Series Descriptive Analysis

Demographic parameters for all eligible cases provided by Capital Health included date of onset, age at onset, sex, laboratory diagnostic information, IMD immunization status at onset and if the case was fatal. The IMD information collection sheet used by Capital Health, modified to include the fields of relevance to this research, is found in Appendix I. A descriptive analysis on these factors is summarized below. No further details on cases beyond this was available.

4.2.1 Temporal Distribution

An epidemic curve (i.e. temporal distribution) of the outbreak cases is seen in Figure 4.1 below. Peak incidence appears to have occurred during the first year of the outbreak, during the first quarters of the years 2000 and 2001. As indicated, IMD incidence returned to baseline levels following June 2002. Recruitment status with respect to this research was included in the distribution; further discussion regarding similarity of recruited and non-recruited cases appears later in the report.

Figure 4.1 Temporal distribution of IMD case series, by recruitment status (n=84)



4.2.2 Age and Sex Distribution

The age distribution of the case series is summarized in Figure 4.2 below. While there was a broad age distribution, most cases in the outbreak were in one of two age cohorts (less than five years of age, 15 to 19 years of age). There was little difference in the sex-specific incidence (51.2% female, 48.8% male). As summarized in Table 4.1, there was also no significant difference in the sex-specific age distribution.

Figure 4.2 Age (at onset) distribution of the IMD case series (n=84)

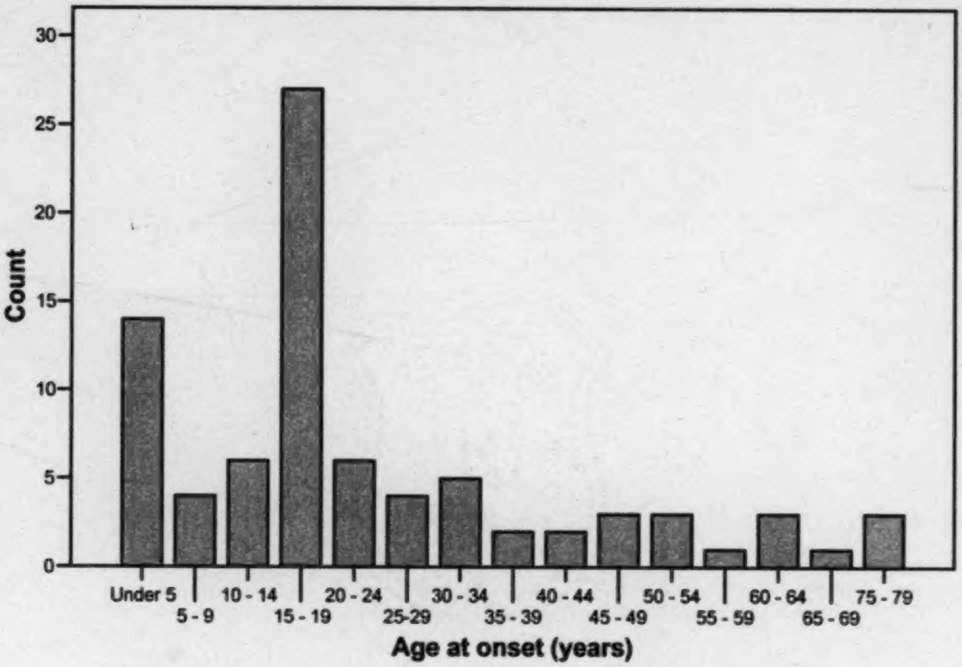


Table 4.1 Descriptive statistics, age (at onset) distribution of the IMD case series (n=84), by sex

Descriptive	Age (years) by Sex			Difference (p-value)*
	Entire group	Male	Female	
Mean	23.85	22.40	24.71	0.584
Median	18.00	19.00	18.00	
Mode	18.00	18.00	18.00	
Standard deviation	19.17	19.03	19.45	
Range	0.13 – 77.00	0.13 – 77.00	0.42-77.00	

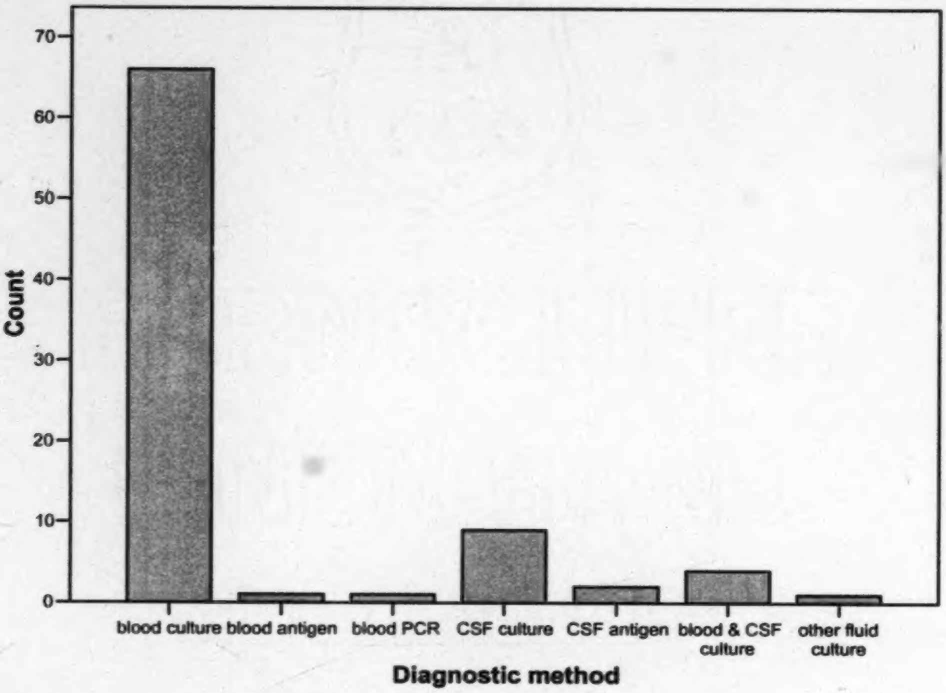
*t-test for equality of means

4.2.3 Clinical Features

4.2.3.1 Diagnostic Method

The method of diagnosis for IMD cases (mutually exclusive categories) is summarized in Figure 4.3 below. *N. meningitidis* was isolated from blood, CSF or another body fluid for 80 of 84 (95%) of cases. The diagnosis for most cases (66/84, 79%) was made through blood culture. A positive antigen test identified three cases (one in blood, two in CSF), and PCR methods, one case.

Figure 4.3 Diagnostic method for IMD cases (n=84)



4.2.3.2 Clinical Manifestation

The proportions of reported clinical manifestations in the IMD case series is summarized in Table 4.2 below. Most cases (72.6%) presented with meningococcemia, 16.7% presented with

Table 4.2 Clinical manifestation of IMD cases (n=84)

IMD Manifestation	Number	Frequency (%)
Meningococcemia	61	72.6
Meningitis	14	16.7
Meningococcemia and meningitis	9	10.7

meningitis, and 10.7% of the case series was clinically consistent with both syndromes. Four cases (4.8%) were fatal. It was reported by Capital Health that approximately 7% of cases (6/84) developed serious non-fatal sequelae (e.g. loss of limbs/digits, hearing loss). However, clinical information was incomplete in this regard, and further analysis was not carried out.

Table 4.3 below summarizes the IMD serogroup distribution for the case series. Most (89%) were serogroup C, a vaccine-preventable serogroup. Six cases were group B, a serogroup for which there was no vaccine available during the outbreak. Two were of unknown serogroup, due to characteristics of the laboratory test used to identify the case. Results of electrophoretic typing (a method of sub-typing within IMD serogroups)[23] for the serogroup C outbreak cases were provided by the provincial public health laboratory.[99] All such isolates were the same genetic clone—electrophoretic type (ET) 15.

Table 4.3 IMD serogroup distribution among entire case series (n=84)

IMD Serogroup	Number	Frequency (%)
Serogroup C	75	89.3
Serogroup B	6	7.1
Serogroup Y	1	1.2
Serogroup C, Y or W-135*	1	1.2
Unknown Serogroup†	1	1.2

*the results of the CSF antigen test for this case precluded more definitive serogrouping
†PCR analysis precluded serogrouping of this case

4.2.4 Description of Recruited Cases and Comparison with Non-recruited Cases

A low recruitment rate can result in recruitment bias. However, the likelihood of this bias severely impacting study validity can be partially assessed by comparing recruited and non-recruited cases on known characteristics that may be potential confounders. Table 4.4 below summarizes statistical assessments that were made on differences in sex, age, fatality rate, IMD serogroup (and predominant serogroup C clone) and IMD immunization status at onset. Descriptively, as compared with non-recruited cases, recruited cases had a higher proportion of males, were slightly younger, less likely to be fatal, more likely to have been immunized for IMD at onset (among those infected with a vaccine-preventable serogroup). Recruited cases were also less likely to have been infected with a vaccine-preventable IMD serogroup or the predominant IMD clone. However, recruited and non-recruited cases were not statistically different from each other on any of these characteristics. As illustrated in the epidemic curve (Figure 4.1 above), the recruited and non-recruited case series did not appear to differ significantly on month of onset.

Table 4.4 Comparison of recruited and non-recruited cases on age, sex, fatality rate, immunization rate, vaccine-preventable serogroup rate

Characteristic	**Mean or proportion**			**Difference (p-value)***
	Entire group	**Recruited**	**Not recruited**	
Age (mean, years)	23.6	23.1	24.1	0.811
Sex (% female)	51.2	47.7	55.0	0.505
Fatality rate (%)	4.8	4.5	5.0	0.922
% immunized before onset among cases with vaccine-preventable IMD serogroup	22.6	29.5	15.0	0.112
% infected with vaccine-preventable IMD serogroup[†]	92.9	90.9	95.0	0.467
% infected with IMD serogroup C/ predominant clone	89.3	86.3	92.5	0.364

*For age, the difference was compared utilizing the t-test for equality of means. For all other comparisons, the Pearson χ^2 test was used.

[†] One case of unknown serogroup was classified as being vaccine-preventable.

4.3 Analysis of Invasive Meningococcal Disease Risk Factor Data Collected in Questionnaire

4.3.1 Questionnaire Responses Resulting in Unknown Exposure Level/status

A total of 132 participants (44 cases, 88 controls) were administered the study questionnaire. The questionnaire included a total of 100 questions; branching resulted in no one participant being asked all 100 questions. Of the 10,873 total questions asked of questionnaire participants, 91 (0.8%) resulted in an unknown exposure level/status, as a result of a "don't know", "not sure" or "refused" question response by study participants, or a missing question response due to interviewer error. Only four question responses in total elicited a refusal; three of these were regarding household income, the fourth, number of kissing contacts. Five question responses were missing, and the remaining 82 of the 91 questions with unknown exposure level/status (90.1%) were a result of a "don't know" or "not sure" response from the participant.

Among the 100 total questions, 56 did not elicit any responses that resulted in an unknown exposure level/status. The proportion of participants with unknown exposure level/status among the 44 questions with at least one unknown exposure level/status is seen in Table 4.5 below. All but five survey questions had less than 5% of participants with unknown exposure level/status. The five survey questions for which 5% or more of participants had unknown exposure level/status were: presence of a humidifier in the home, household income, sharing of pipe or vessel when smoking or inhaling substances other than tobacco, and onset fever/new cough in month of interest in case group participants.

Table 4.5 Proportion of participants for which exposure level/status measured by a given survey question is unknown, among survey questions for which the exposure level/status of at least one participant is unknown (n=44)

Proportion of participants for which exposure level/status measured by a given survey question is unknown*	**Number of survey questions with the given frequency of participants with unknown exposure level/status**
Less than 1%	17
1 – 4.99%	22
5-10%	5

*exposure level/status was unknown when participants provided a "don't know/not sure" response to a survey question, the participant refused to provide a response, or if the response was blank (interviewer error)

4.3.2 Descriptive Analysis

4.3.2.1 Summary of Risk Factor Information Collected from Cases and Controls

A descriptive summary of exposure level/status for the 67 risk factors evaluated in both cases and controls is found in Appendix J. Categorical variables are described in terms of presence/absence of the risk factor within each 1:2 case-control triad; for continuous variables, the mean level of the exposure in cases and controls is presented. Twelve risk factors exhibited "complete separation", that is, lacked a discordant pair in the numerator and/or the denominator of the Mantel-Haenszel matched odds ratio expression, five of which (asplenia, complement disorder, a kidney disease requiring dialysis or HIV) had neither a case nor control possessing the factor. Complete separation impacted the univariate and multivariate analysis on these factors, as will be discussed.

4.3.2.2 Reported Chronic Health Conditions

Approximately 11% of cases and 30% of controls reported having a health condition other than six specific diseases (asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, HIV) asked about. Information on specific "other" chronic health conditions was collected with an open-ended question in the instrument. A summary of responses is presented in Table 4.6 below.

Table 4.6 Other chronic health conditions self-reported by participants

Chronic health condition	Cases (n=44)		Controls (n=88)	
	No.	%	No.	%
Asthma	2	4.5	9	10.2
Cardiovascular disease	1	2.3	5	5.7
Ear infection	1	2.3	1	1.1
Allergies	1	2.3	2	2.3
Other*	0	0.0	9	10.2

*Other reported conditions included sleep apnea, neuropathy, migraine headaches, diverticular disease, rheumatoid arthritis, ADHD

4.3.2.3 Invasive Meningococcal Disease Immunization Status and Stated Reason for Not Being Immunized

As indicated, IMD immunization was offered and recommended by Capital Health to residents of the region aged two to 24 years, in 2000 and 2001. In both the case and control participant group, 61.4% (27 and 54 participants, respectively) were of an age eligible to have received the vaccine during the immunization campaigns. As summarized in Table 4.7 below, cases were significantly less likely to report having received the IMD immunization. If it is assumed that "don't know/not sure" eligible control group participants actually received the vaccine, the immunization rate in this group is 85%, within 1 percent of the reported IMD immunization rate for eligible residents of the entire Capital Health region.[22] Again, the immunization status presented in Table 4.7 was not used in the univariate analysis, as it does not account for vaccine-ineffective IMD serogroups and the timing of immunization in relation to IMD onset.

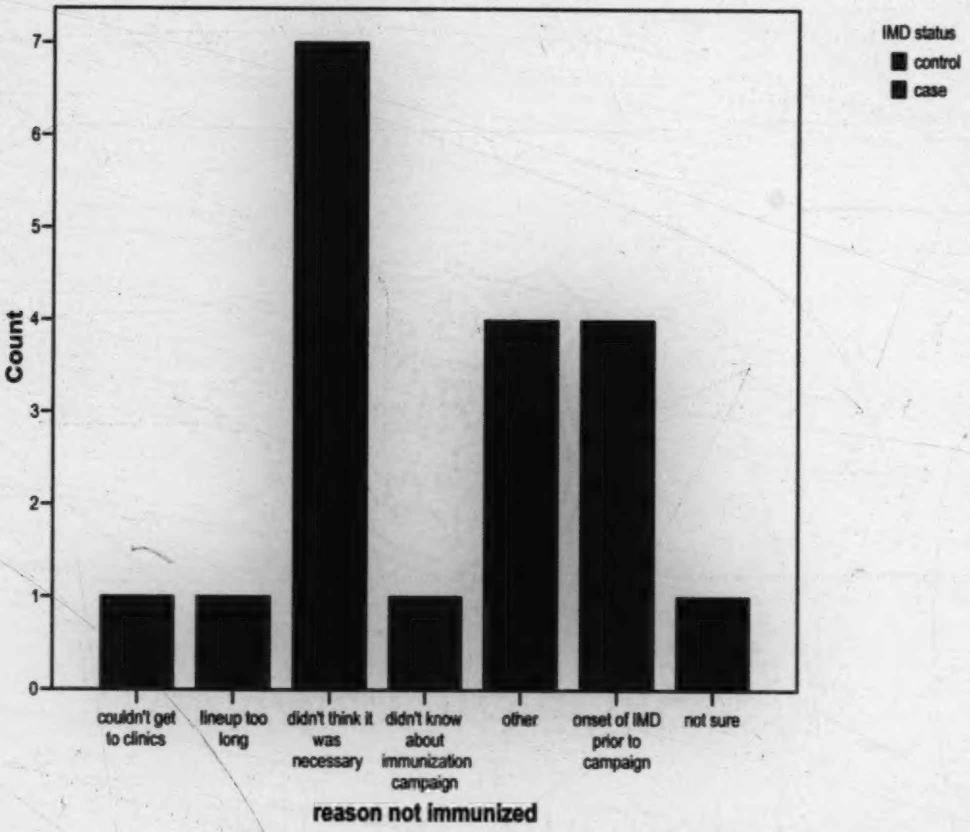
Table 4.7 Immunization status of study participants eligible to receive IMD vaccine

Immunization Status	**Cases (n=27)**		**Controls (n=54)**		**Difference* (p-value)**
	No.	**%**	**No.**	**%**	
Immunized	16	59.3	43	79.6	0.009
Not immunized	11	40.7	8	14.8	
Don't know/not sure	0	0.00	3	5.6	

*Pearson χ^2 test.

The stated reasons for not being immunized for vaccine-eligible study participants that were not immunized (19 participants in total) are summarized in Figure 4.4 below. The most frequently cited reason for participants was that they didn't think immunization was necessary. An important reason in the case group was that IMD onset occurred prior to the start of the campaign—a number of IMD "index cases" during the period December 1999 to February 2000 alerted public health officials to the outbreak and elicited the immunization campaign. "Other" reasons for not being immunized included participant physician advising that the immunization was not necessary, that a clinic ran out of vaccine and the participant didn't return another time, and that the participant "didn't want it".

Figure 4.4 Stated reason for not receiving IMD immunization among vaccine-eligible participants (n=19)



4.3.2.4 Change in Invasive Meningococcal Disease Risk Behaviors After Onset

Changes in three IMD risk behaviors were assessed after the month of interest: active smoking, passive smoking outside the home, and bar attendance (see Table 4.8 below). Of those reporting having engaged in these behaviors, a slightly higher proportion of controls reported a reduction in frequency in these behaviors after the month of interest. However, none of these differences were statistically significant.

Table 4.8 Participants reporting reduction in selected IMD risk factors after month of interest*

Risk Behavior	Cases		Controls		Difference† (p-value)
	No.	%	No.	%	
Active smoking	4	33.3	6	35.3	0.913
Passive smoking outside home	19	57.6	31	58.5	0.933
Bar attendance	15	68.2	18	69.2	0.938

*Among participants that reported engaging in the risk factor at least once per month during the the month of interest

†Pearson χ^2 test

4.3.2.5 Exposures Measured Among Cases Only

Six risk factors were measured among cases only; a descriptive summary of responses is found in Table 4.9 below. Nearly three quarters of cases reported sharing a beverage from the same cup or glass, or from the same straw, bottle or can as someone else during the month of interest. Approximately seven percent of cases reportedly had onset of fever and cough during the month of interest, however, this was exceeded by the proportion of unknown responses. Sharing of a toothbrush was relatively rare, but sharing of other articles (lipstick/lip balm, eating utensils) was more common.

Table 4.9 Summary of exposure frequencies for factors measured among cases only (n=44)

Exposure*	Yes		No		Don't know or not sure	
	No.	%	No.	%	No.	%
Shared beverage from same cup or glass without washing it first	32	72.7	9	20.5	3	6.81
Drank from same straw, bottle or can as someone else	32	72.7	11	25.0	1	2.27
Used same toothbrush as someone else	2	4.54	41	93.2	1	2.27
Used the same fork, knife or spoon without washing it first	12	27.3	32	72.7	0	0.00
Shared the same lipstick or lip balm as someone else	11	25.0	32	72.7	1	2.27
Onset of fever and new cough	3	6.81	37	84.1	4	9.09

*During month before onset

4.3.3 Univariate Analysis, Modifiable Invasive Meningococcal Disease Risk Factors

Several variables in the questionnaire were not included in the univariate analysis for IMD risk factors. The first category of excluded variables are those corresponding to exposures that did not necessarily occur during the month of interest. These include questions regarding change in risk behaviors (i.e. passive, active smoking) after the month of interest, and questions that were used in cueing and narrowing the exposure window of interest, that assessed exposure during the participant's entire life, or in the year of the month of interest. The second category of variables excluded from univariate analysis were those for which none of the case nor control participants had the risk factor being measured, all of which pertained to specific health conditions of importance for IMD risk. These included asplenia, complement disorder, a kidney disease requiring dialysis or HIV prior to the month of interest.

Of all exposures included in the univariate analysis, eight were significantly associated with IMD, as seen in Table 4.10 below. Six of these exposures had been measured for all age cohorts. Three of these exposures (furnace humidifier, church attendance, chronic health condition) were protective. Rave attendance among those 12 and older at onset, and frequency of bar attendance among those 16 years of age and older at onset were both positive associations. There were no significant associations among exposures measured exclusively in participants less than five years of age at onset. Vaccine-mediated immunity was not significantly protective (OR=0.761; 95% confidence interval, 0.217 – 2.674).

4.3.4 Development of Logistic Regression Model

A summary of the model-building strategy is found in Appendix K. Some variables included in the first model exhibited instability, that is, the value of the upper limit of the 95% confidence interval was above 100. This is a function of the low cell counts for these variables, as is illustrated in the numbers of cases and controls with (or without) the exposure for variables in first model (Table 4.11 below). Unstable variables were initially excluded from the reduced model. However, none of the remaining variables exhibited statistical significance and thus the reduced model was re-fitted including the unstable variables. Four variables initially removed from the first model were found to be statistical counfounders (i.e. they significantly affected the β coefficients of other variables in the model) when added back to the model individually, and thus were included in subsequent models. The final step in model building was a test for

Table 4.10 Exposures significantly associated with IMD, univariate analysis

Exposure[a]	**Odds ratio**[b]		**95% confidence interval**	**p-value**[c]
Participant lived in Canada for all of his/her life	10.0		1.23 – 81.4	0.03
Participant's home was heated with a furnace that had a humidifier attached	0.32		0.12 – 0.83	0.02
Participant had chronic health condition (other than six conditions specifically asked)[d] prior to month of interest	0.25		0.07 – 0.88	0.03
Participant's mother lived in participant's home and participant's mother was a smoker	3.84		1.18 – 12.5	0.03
Frequency of visits by participant to places outside participant's home where other people were smoking	<1/month:	1.00		
	≥1 month,<1/week:	2.40	0.68 – 8.50	0.17
	≥1/week:	2.93	1.09 – 7.86	0.03
Participant attended a service at a church, synagogue or mosque	0.36		0.17 – 0.76	0.008
Participant attended rave[e]	4.88		1.28 – 18.6	0.02
Participant visited bars or other establishments where alcoholic drinks are served more than once in a month[f]	16.0		2.06-124	0.008

[a] during month of interest, unless otherwise stated

[b] odds ratio for exposure, relative to reference category of no exposure (odds ratio=1.00), unless otherwise stated

[c] Wald statistic, χ^2 distribution

[d] conditions other than asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, or HIV

[e] exposure information collected only from participants ≥12 years of age at onset (cases) or equivalent calendar month (controls)

[f] exposure information collected only from participants ≥16 years age at onset (cases) or equivalent calendar month (controls)

Table 4.11 Exposure distribution for cases and controls, variables in first multivariate model

Exposure[a]	**Number, Frequency (%)**[c]			
	Cases (n=44)		**Controls (n=88)**	
	No.	**%**	**No.**	**%**
Lived in Canada entire life	42	95.5	72	81.8
Home heated by furnace	35	79.5	77	87.5
Humidifier on furnace	12	27.3	42	47.7
Other humidifier used in home	6	13.6	20	22.7
Vaccine-mediated immunity	11	25.0	26	29.5
Diabetes	2	4.54	1	1.14
Chronic health condition[b]	5	11.4	25	28.4
Age in months, when breastfeeding stopped[c, d]	0.78	0.35	1.77	0.65
Mother of participant did not complete high school[d]	4	9.09	3	3.41
Lived with mother that smoked	11	25.0	9	10.2
Number of smokers that lived in the participant's home[c]	0.70	0.151	0.50	0.08
Smoked/inhaled something other than tobacco	9	25.0	10	11.4
Kissed someone on lips	35	79.5	61	69.3
Attended service at a church, synagogue or mosque	12	27.3	48	54.5
Attended a rave[e]	8	18.2	4	4.54
Went to a bar or other establishment where alcoholic drinks served[f]	23	52.3	26	29.5
Visited place(s) outside the home where other people smoking				
<1/month	10	22.7	35	39.8
≥1 month,<1/week	8	18.2	15	17.0
≥1/week	26	59.1	38	43.2
Smoked cigarettes at least once per month[e]	12	27.3	17	19.3

[a] during month of interest, unless otherwise stated

[b] conditions other than asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, or HIV

[c] for continuous variables, mean and standard error of mean are shown

[d] exposure information collected only from participants less than five years of age at onset (cases) or equivalent calendar month (controls)

[e] exposure information collected only from participants ≥12 years of age at onset (cases) or equivalent calendar month (controls)

[f] exposure information collected only from participants ≥16 years age at onset (cases) or equivalent calendar month (controls)

interaction among factors in the model. Five plausible interactions were tested, with none achieving statistical significance. The final multivariate model is seen in Table 4.12 below.

Two of the confounders were continuous variables. The logistic model assumes a linear relationship between model β values and levels of the variable (e.g. at the midpoint between each quartile), and thus it must be confirmed if continuous variables meet this assumption. For both continuous variables, a quadratic relationship was observed, and thus a change in scale was warranted. Because the median variable for both models was zero, dichotomous variables corresponding to the continuous variable (presence/absence of breastfeeding in place of number of months breastfed, and presence absence of smokers in the participant's dwelling in place of number of smokers in the dwelling) were fitted into the model. The breastfeeding dichotomous variable exhibited complete separation, and thus was removed.

Three factors significant in univariate analysis (rave attendance, bar attendance, residing with mother that was a smoker) were also significant after multivariate analysis. These factors exhibited instability (i.e. large value at upper end of 95% confidence interval) and thus the associations should be interpreted with caution. Four factors significant after univariate analysis (lifetime residence in Canada, presence of other chronic health condition, humidifier attached to furnace, church attendance) were not significant in multivariate analysis. One factor not significant in the univariate analysis (use of humidifier not attached to a furnace) was significant at the multivariate stage. Three statistical counfounders (mother's education level, passive exposure to cigarette smoke outside the home, and number of smokers in the home) were kept in the final model. Vaccine-mediated immunity, as in univariate analysis, was not a significant predictor even when forced into the multivariate model.

4.3.5 Sub-analysis, Modifiable Invasive Meningococcal Disease Risk Factors for Serogroup C Cases Only

Univariate analysis including only serogroup C cases (Table 4.13) revealed similar risk associations to those identified among the entire case series. No exposures were found to be significant that were not significant in the entire case series, and only one variable significant for the entire case series (presence of other chronic health condition) was not significant among serogroup C cases. The risk estimates and 95% confidence intervals were also similar among significant exposures. Multivariate analysis (using the same model-building process as used for the entire study group data set) revealed no statistically significant risk factors among the

Table 4.12 Final multivariate model

Exposure[a]	Odds ratio[b]	95% confidence interval	p-value[c]
Humidifier (not attached to furnace) sometimes used in participant's dwelling	0.06	0.006 – 0.60	0.02
Participant's mother lived in participant's home and participant's mother was a smoker	23.6	3.03 – 184	0.003
Participant attended rave[d]	23.7	2.28 – 246	0.008
Participant visited bars or other establishments where alcoholic drinks are served more than once in a month[e]	47.3	3.42 – 656	0.004
Highest level of education less than high school diploma for participant's mother[f]	7.31	0.70 – 76.8	0.10
Frequency of visits by participant to places outside participant's home where other people were smoking[f,g]	<1/month: 1.00		
	≥1 month,<1/week: 3.48	0.68 – 17.9	0.14
	≥1/week: 1.16	0.28 – 4.87	0.84
Participant resided with smoker(s)[f]	0.28	0.07 – 1.05	0.06
Vaccine-mediated immunity[h]	1.22	0.22 – 6.79	0.82

[a] during month of interest, unless otherwise stated

[b] odds ratio for exposure, relative to reference category of no exposure (odds ratio=1.00), unless otherwise stated

[c] Wald statistic, χ^2 distribution

[d] exposure information collected from participants ≥12 years of age at onset (cases) or equivalent calendar month (controls)

[e] exposure information collected from participants ≥16 years age at onset (cases) or equivalent calendar month (controls)

[f] included in the model due to statistical confounding

[g] exposure information collected from participants <18 years age at onset (cases) or equivalent calendar month (controls)

[h] forced into the model

Table 4.13 Exposures significantly associated with IMD among serogroup C cases only, univariate analysis

Exposure[a]	Odds ratio[b]		95% confidence interval	p-value[c]
Participant lived in Canada for all of his/her life	10.0		1.23 – 81.4	0.031
Participant's home was heated with a furnace that had a humidifier attached	0.39		0.098 – 0.94	0.018
Participant's mother lived in participant's home and participant's mother was a smoker	4.85		1.29 – 18.2	0.019
Frequency of visits by participant to places outside participant's home where other people were smoking	<1/month:	1.00		
	≥1 month,<1/week:	2.68	0.72 – 10.0	0.14
	≥1/week:	3.04	1.05 – 8.83	0.041
Participant attended a service at a church, synagogue or mosque	0.29		0.12 – 0.70	0.006
Participant attended rave[e]	4.22		1.08 – 16.5	0.039
Participant visited bars or other establishments where alcoholic drinks are served more than once in a month[f]	16.0		2.06-124	0.008

[a] during month of interest, unless otherwise stated

[b] odds ratio for exposure, relative to reference category of no exposure (odds ratio=1.00), unless otherwise stated

[c] Wald statistic, χ^2 distribution

[d] conditions other than asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, or HIV

[e] exposure information collected only from participants ≥12 years of age at onset (cases) or equivalent calendar month (controls)

[f] exposure information collected only from participants ≥16 years age at onset (cases) or equivalent calendar month (controls)

serogroup C cases. There were no significant associations in the first fitted model (which included all variables with a likelihood ratio test p-value below 0.25), and thus no further model building was conducted.

CHAPTER 5: DISCUSSION

5.1 Case Series

5.1.1 Age, Sex, and Temporal Distribution

The age, sex and temporal distribution of the case series are generally consistent with those reported for IMD cases in other populations. As observed globally, two peaks were observed in the age distribution of IMD cases, in the less than five-year and the 15 – 19-year age cohorts. However, it was the latter cohort with the highest age-specific incidence in this outbreak, rather than the former, as has recently been observed nationally[4] and worldwide.[16] This has important implications for age-associated modifiable IMD risk factors, which will be discussed later. Sex-associated IMD risk is not evident in this case series. There was no significant difference in sex-specific incidence, or (contrary to recent nationwide IMD epidemiology in Canada)[4] in the sex-specific age distribution. IMD incidence appeared to be highest during the winter months of the outbreak, which is also consistent with national[4] and international[14] surveillance.

5.1.2 Clinical Characteristics

The case fatality rate in this case series (approximately 5%) was lower than national rates in Canada during 1999-2001,[4] and those reported globally over the last two decades[11] (both approximately 10%). While it is known that several outbreak cases had onset of serious IMD-associated sequelae, comprehensive data in this regard were not available for this research. Serogroup epidemiology was consistent with trends observed in North America and Canada, with most cases caused by serogroups B and C. However, serogroup C was clearly predominant in the Capital Health outbreak, accounting for approximately 90% of cases; nationwide, group C accounted for 51 and 59% of cases nationwide in 2000 and 2001, respectively.[4] This was fortunate from a public health perspective, in that this serogroup was and is vaccine preventable, making the mass immunization campaign a viable strategy in controlling the outbreak. All serogroup C isolates were of a genetic clone (ET-15) that was first observed in Canada in 1986;[23] between 1999 and 2001 over 90% of serogroup C isolates in Canada were of this same sub-type.[4] No risk factors unique to cases of this sub-type were identified in this research, the sub analysis for which was hampered by the low number of cases in the study population and the high frequency of outbreak cases infected with the same IMD clone.

Approximately 73% of the case series had a clinical course described as "meningococcemia", the most severe manifestation of IMD. While the validity of syndromic classification of the IMD cases could not be confirmed with information available to the researcher, this proportion is significantly higher than is reported in the literature (15-20%).[11] This clinical phenomenon may be worthy of future research.

5.2 Modifiable Risk Factors

Passive exposure to environmental tobacco smoke both inside and outside the home appear to be important risk factors for IMD, consistent with other key studies. Physiological mechanisms may directly explain this association. Cigarette smoke is thought to promote adherence of bacterial pathogens (including *N. meningitidis*) to the buccal epithelium[78] and compromise mucosal immunity.[79,80] This exposure may also be a cofactor for disease, as a result of increased risk of respiratory tract infections,[81] which, as discussed, have also been shown to increase IMD risk. The specific association with exposure to a mother (and not a father or other household member) that smokes is also consistent with other key IMD studies, and with research suggesting that maternal smoking contributes more to overall passive tobacco smoke exposure in children than paternal smoking.[82] Tobacco smoke has also been cited as a risk factor for carriage of meningococcal bacteria,[8,83,84,85,86] and thus, exposure to smokers may the increase in the likelihood of exposure to the pathogen, contributing to increased IMD risk.

Active smoking was not identified as a significant risk factor in this research, consistent with findings in other research. Smoking status was not identified as a significant risk factor after multivariate analysis in three key IMD risk factor studies.[30,34,38] However, passive smoking was a significant risk factor in all three studies, with a stronger association in child age cohorts. It appears likely that passive exposure to tobacco smoke in children, who are at higher risk of IMD infection, is more important for IMD risk in the population than active smoking in adolescents or adults. Statistical power limitations precluded further age subgroup analysis in this research.

While attendance at bars has been previously cited as an IMD risk factor, this is the first epidemiologic study to identify participation at "rave" events as a risk factor for IMD or any other infectious disease. During 2000, there were thought to be at least four rave clubs operating in Edmonton, with monthly attendance in the thousands,[87] and, as discussed, attendance at one particular rave event was one of the few epidemiologic links identified by public health officials among cases in the outbreak. While it is not known whether behaviors associated with these events (including the use of methamphetamines such as "ecstasy")[88] contribute to risk (e.g. by causing excessive thirst[108] and a possible increase in sharing of beverages), raves may present a risk similar to attendance at "discos", for which there is an observational IMD association, as discussed. Crowding in bar and rave facilities may ultimately be responsible for increased IMD risk, because such conditions promote respiratory droplet transmission and passive exposure to tobacco smoke.[40] The importance of the latter of these two factors is consistent with the significant influence that the non-dwelling passive smoking variable had on the β coefficient for rave attendance when fitted into to the multivariate model.

Use of a humidifier in the home (univariate, furnace humidifier; multivariate, non-furnace humidifier) was found to be protective. While use of a humidifier may be colinear with other factors such as socioeconomic status, this is consistent with other research (cited earlier) that identified low humidity as a risk factor for IMD. Humidity may also act as a cofactor with antecedent respiratory infection. Influenza virus, which can increase IMD risk in those infected, is known to survive better in low humidity environments.[89] Antecedent respiratory infection in study participants could not be controlled for in the analysis, and thus the independent protective effect of humidity could not be calculated.

Household crowding, an important IMD risk factor in other key research, was not associated with increased IMD risk in this study. This applies to each of the surrogate crowding measures used, including number of household residents, number of bedrooms, bedroom sharing and persons per bedroom. It may be, as has been suggested elsewhere,[57] that only a severe, threshold level of household crowding will result in additional IMD risk. In the case group for this study, the mean number of persons per bedroom was 1.07, which would not be considered indicative of a "crowded" dwelling. While different measures of crowding were used in the key IMD studies, it would appear that household densities among IMD cases in the source population for this study are significantly lower. In one key study, increased IMD risk was observed only at densities of greater than 2.5 persons per bedroom[39] and in another study where household crowding was observed as an IMD risk factor, the proportion of cases that shared a bed was 72%.[32] The level of household crowding in IMD cases for this study may not have resulted in sufficient close contact with other household residents to appreciably increase disease transmission risk.

The positive (univariate) association between lifetime residence in Canada and IMD status would seem to contradict travel-associated IMD risk reported in the literature. However, the association is plausible. As indicated, asymptomatic colonization with *N. meningitidis* can confer immunity in the carrier. Carriage rates of virulent strains of this pathogen may be relatively low in Canada even during periods of higher disease incidence, which may result in increased susceptibility in the population during outbreaks.[90] Those that moved to Canada from a population with higher virulent strain carriage may have increased immunity relative to lifetime Canadian residents. Information on country of origin was not collected from immigrant participants, and thus, it could not be confirmed if these individuals arrived from an area of higher meningococcal carriage.

The protective (univariate) association of a self-identified chronic health condition other than those specifically asked about in the instrument would also seem contradictory. As indicated, when asked to specify the chronic health condition, most reported either asthma or cardiovascular disease. These conditions are not reported IMD risk factors, and thus one would not expect a positive association. It may be that these disease conditions exhibit colinearity with other IMD risk factors, i.e. those in poorer health may be less likely to engage in IMD risk behaviors. The finding may also be a result of aggregation bias, in that very different health conditions were collapsed into one dichotomous variable, potentially affecting the validity of the risk association.

The protective association with church attendance identified in univariate analysis was also consistent with other IMD research. The negative association between church attendance and other important IMD risk factors such as smoking status[91,92,93] may explain this finding. The loss of significance upon fitting this variable into the first multivariate model may be indicative of colinearity with other risk factors.

Exposure to saliva through lip kissing or sharing of articles contaminated with saliva was not assessed in this study; only the fact of lip kissing was assessed. Lip kisses with a low degree of salivary contact may have masked the risk from kisses that resulted in more significant salivary exposure. Case group participants frequently reported the sharing of articles such as beverage vessels, eating utensils and lipstick. Poor recall by questionnaire pretest control group participants precluded the collection of information on this risk factors from controls in the study proper, and thus a risk measure could not be calculated. The validity of recall of such behaviors during a specific one-month period several years previously may be low even in the case group. However, the importance of saliva on shared objects as an IMD transmission vehicle has been called into question. It has been reported in recent research that the prevalence of *N. meningitidis* carriage in saliva is low, even when compared with carriage rates in the nasopharynx[106] and that sharing of beverage vessels and cigarettes is not important in *N. meningitidis* acquisition.[9] Sharing of cigarettes and vessels used for smoking of substances other than tobacco was also not identified as IMD risk factors in this study. Further research is needed to assess the significance of salivary IMD transmission.

Vaccine-mediated IMD immunity was not protective in the study group. Recruitment bias did not appear to significantly contribute to this finding, as recruited and non-recruited cases were similar on this factor, and the proportion of control group participants immunized among those eligible for IMD immunization was similar to the entire study population. IMD immunization status and timing (i.e. before IMD onset (cases) or equivalent month for (controls)) was self-reported, and thus recall and/or measurement bias cannot be ruled out. Assuming immunization status was free from bias, using the study data to calculate vaccine effectiveness may remain invalid. A period of approximately two weeks is generally needed for generation of an antibody response post IMD immunization;[19] it was not determined if any of the cases received their immunization within two weeks of onset. The data set for this study also includes several cases that had onset prior to the start of the immunization campaign, inclusion of whom could bias the vaccine effectiveness measure.

Ultimately, the lack of a statistically significant protective association may be a result of low statistical power. While the case-control study is not the preferred design for evaluating vaccine effectiveness, it can be calculated (1-OR).[102] Thus, the vaccine effectiveness in the study group (based on the univariate OR point estimate—the multivariate OR was above 1.0) was 23.9% (1 – 0.761)%. However, there was a wide confidence interval around this point estimate. It has been observed that IMD polysaccharide vaccines, while effective in controlling serogroup C IMD outbreaks, are only 65% effective after two years in children and young adults.[100] This is within the 95% confidence interval for vaccine effectiveness in the study group, or 0 to 78.3%, as calculated by (1 – 0.217,2.674). The effectiveness of the IMD immunization campaign in the Capital Health region was not investigated in this study, and thus would seem worthwhile for future research.

Case and control group participants were equally as likely to have reported a change in IMD risk behaviors following the month of interest. It may be that cases were not cognizant of modifiable IMD risk factors and resumed like lifestyle patterns after recovery from the infection. However, information regarding IMD sequelae was not collected in the questionnaire, and thus it is unknown whether separate analysis of cases fully recovered and cases recovered with sequelae would have yielded the same result.

5.3 Limitations

5.3.1 Study Design

Case-control was the design of choice for this study from a feasibility perspective, mainly the result of the relative rarity of IMD in the source population. The baseline incidence rate was less than one per 100,000, and even during the year 2000, when the highest IMD incidence was observed during the outbreak in the Capital Health region, the incidence rate in the population was approximately five per 100,000. Thus, even if this study had been conducted during the outbreak, a cohort design would have been impractical. An observational study design was necessary from a practical and ethical perspective, as the nature of the exposures under study (e.g. smoking) would have precluded their random assignment to study participants.

The case-control design is subject to several validity threats. Rather than comparing absolute rates of disease among exposed and unexposed in the source population to quantify risk (as in a cohort study), a control group is selected to estimate the relative distribution of exposure in the population, yielding a relative measure of effect.[95] Thus, the validity of the effect measures derived from case-control studies is dependent upon selecting a control group that does not (other than randomly) differ with respect to distribution of exposure from the case source population. The method of control recruitment in this study does not ensure that the control group achieves this characteristic.

5.3.2 Telephone-Based Recruitment

The use of the telephone in recruiting and surveying study participants may also be a limitation. Essentially, to participate in the study, cases required a residential telephone number at which they could be contacted, and controls, a residential "landline" telephone. However, cases that were not contacted by telephone were also sent a recruitment letter, meaning, in theory, they had the opportunity to contact the researcher from an alternate telephone if the letter was received by the potential participant (no participants did so, however). In effect, then, this was a study eligibility criterion.

While this eligibility requirement preserved internal validity, it may have introduced recruitment bias. A recent (2002) Statistics Canada nationwide survey reported that 97% of Canadian households had at least one telephone.[96] If this is used as a proxy for the source population, study controls differed from the source population on this factor. Households without telephones differ from the source population on several characteristics related to health status, including family income and level of education in adult members.[97] In addition, an emerging limitation of random-digit dialing is the increasing use of cellular telephones. In 2004, it was estimated that approximately three hundred thousand Canadian households (2.4% of all households) had only a cellular telephone number, an increase of 29.6% from 2003.[104] Individuals living in such households were precluded from recruitment as control group participants, because the sampling frames for this research (and most current random-digit dialed household surveys)[105] were limited to landline telephones. The effect of this bias cannot be assessed, as it is not known whether any of the eligible participants did not have access to a residential landline telephone at the time of study recruitment.

The use of random-digit dialing to recruit controls may have introduced bias (nonresponse bias) into the results. Approximately half of all randomly generated household telephone numbers used did not yield a recruit, as a result of initial refusal to participate by the individual answering the telephone, or, the telephone number at a household never being answered. It is possible, and perhaps probable, that individuals that answered the telephone and completed the eligibility questionnaire differed from the source population with respect to at least some of the exposures under study. For example, it has been observed that recruited research survey participants are often of higher socioeconomic status than non-recruits.[101]

Telephone recruitment of controls also contributed to study efficiency (and cost) of the study. Fewer than 1% of randomly generated telephone numbers contacted yielded a control group participant. Approximately half of the randomly generated telephone numbers reached households, a result of the characteristics of the telephone number blocks provided to the PRL by the local telephone service provider. Of those households reached, approximately one third refused administration of the eligibility questionnaire.

5.3.3 Matching

A limitation of the study is also the relative inefficiency in recruitment of controls introduced by matching. Narrow matching criteria were used to ensure desired stratification on important confounders. However, this contributed to the low recruitment rate—approximately half of all households contacted had no resident that met the age/matching criteria, and only 5% households to which the eligibility questionnaire was administered had a resident that met matching requirements and was subsequently recruited. Matching and the limitations associated with telephone recruitment outlined above contributed to a higher than anticipated financial cost of recruiting control group participants for the study. Future population-based case-control studies utilizing like study eligibility criteria and recruitment methods in Alberta should anticipate a like level of efficiency, and a recruitment unit cost in excess of $125 CDN per control group participant.

5.3.4 Case Recruitment

The case recruitment rate, which was lower than anticipated, is an important consideration in assessing the validity of this research. Only slightly above half of eligible cases were recruited and administered the study instrument. While recruited and non-recruited cases were not statistically different on age, sex, IMD fatality rate, IMD immunization status and IMD serogroup, differences on other important IMD risk factors (e.g. socioeconomic status) could not be assessed. The main limiting factor in case recruitment was locating a telephone number at which the potential participant could be reached. A significant number of potential case participants did not return recruitment phone calls and/or letters, which may represent tacit refusal to participate, or, an incorrect telephone number or address. It is probable that those cases that had a change in telephone number between time of diagnosis and time of study recruitment, or received telephone messages and/or letters regarding the study and chose not to respond, were significantly different from successfully recruited cases on important IMD risk factors. Resultant nonresponse bias may have significantly impacted the study validity.

It was unfortunate (and significant in terms of study validity) that seven of the 51 cases successfully recruited at the first stage were lost to follow-up at the second stage. A time lapse of several months between the first and second stage of case recruitment was likely an important contributing factor in the loss of these cases. This delay occurred as a result of study resource constraints; the researcher, employed full time during the entire research study, was unable to conduct second stage recruitment concurrently with control group recruitment, and thus, case recruitment was deferred. The seven lost cases resulted in a significant reduction in statistical power. The efficiency of this research was also negatively impacted, as 14 control participants, first stage recruited by the PRL for these lost cases, could not be used in the study.

5.3.5 Case Ascertainment

Case ascertainment bias should be considered when assessing the validity of the study results. A cascade of factors influenced the likelihood that a case of IMD was detected through public health surveillance in the study population. Each reported IMD case required onset of clinical signs, physician consultation through which a threshold index of suspicion for IMD resulted, collection of an appropriate clinical sample (prior to antibiotic administration) for which meningococcal laboratory testing was ordered, a positive test result, and report of the result to public health. Variability in surveillance sensitivity (that is, the extent to which all or most cases in a given population are identified)[107] exists at each step in the continuum. It is not known what proportion of all IMD cases in the source population were identified through surveillance.

It is likely that an important factor biasing case ascertainment was the timing of clinical sample collection from suspected IMD cases. Following identification of the outbreak in the Capital Health region, the index of suspicion for IMD was likely heightened among area clinicians. If so, the sensitivity of identification of probable clinical IMD cases among individuals presenting to regional physicians with the distinctive clinical presentation for IMD (especially meningococcemia) would likely have been high. However, a significant proportion of outbreak IMD cases may not have been laboratory confirmed. The rapid progression of the disease necessitates prompt initiation of antibiotic therapy for suspected cases, which can significantly lower the sensitivity of bacterial culture if the clinical sample is not collected prior to antibiotic administration.[11] There were reportedly several probable clinical IMD cases in the region during the course of the outbreak that were not laboratory confirmed for this reason,[103] which reduced the case series population and study power. These non-confirmed cases may have differed significantly from laboratory confirmed cases (e.g. more clinically severe cases may have been administered antibiotics sooner than less severe); if present, such differences could also have biased the results.

5.3.6 Potential Recall Bias

The length of time between questionnaire administration and the one-month exposure window of interest is a threat to validity for this research. Study participants were asked to report on point exposures that took place on average more than three years in the past. This likely influenced validity of responses provided by study participants. If the magnitude of the bias were approximately equal in the case and control group, the measure of effect would generally be biased towards the null. However, this assumption cannot be made, as onset of IMD in cases (the basis for the exposure period) may have resulted in superior recall as compared with control group participants. Information regarding one important IMD risk factor, antecedent respiratory tract infection, was not asked of controls as a result of poor recall demonstrated during the pretest of the instrument. Thus, this factor could not be controlled for in the multivariate analysis.

5.3.7 Survey Instrument

While the instrument used in the research was adapted from several validated questionnaires used in similar IMD studies, no one validated questionnaire was found that included all constructs of relevance to this research. Content validity for complex constructs in the instrument such as "life stress" is difficult to assess. Many exposures included were of high face validity, such as presence/absence of significant life events such as international travel. However, the extent to which the method used to calculate household density achieved construct validity for household crowding as a risk factor for IMD cannot be determined. Criterion validity could not be assessed for the instrument, as there is no "gold standard" to which the instrument can be compared.

Additional threats to validity were associated with the manner in which the questionnaire was administered. The researcher was not (and could not be, due to the nature of the methods) blinded to IMD status of participants during questionnaire administration, and thus it cannot be confirmed if the responses were free from interviewer bias. It was ensured to the extent practicable that the survey responses of participants 12 to 17 years of age were made in private, to prevent responses biased by the presence of a parent or guardian. However, it could not be confirmed over the telephone that the parent or guardian had actually moved to an area where the interviewer's questions or the answers given by the child could not be heard as had been requested, and therefore the validity of these responses cannot be assured.

The reliability of the questionnaire information was maximized as possible. Though pre-tested, the test-retest reliability of the instrument was not assessed. One individual (the researcher) developed and administered the questionnaire, and coded, cleaned, entered and analyzed the data, and the instrument itself was comprised mainly of closed ended dichotomous or polychotomous responses. This likely served to achieve high reliability.

5.3.8 Study Power

The relatively low number of study participants resulted in limited statistical study power, and unstable risk estimates in the regression analyses. In spite of this, risk effects above (positive associations) and below (negative associations) the detection limits were found for several of the exposures under study. These included age-dependent exposures measured only within specific age cohorts, such as those 12 years (e.g. rave attendance) or 16 years (e.g. bar attendance) of age at onset, which were of reduced power in relation to those measured among all study participants. However, for those exposures measured only among participants less than five years of age at onset, the study power precluded detection of negative (protective) associations. Thus, the protective effect of early childhood exposures such as day care facility attendance and breastfeeding could not be assessed through this research.

Statistical power limitations were evident in the multivariate analysis. Several potentially important variables exhibited complete separation and were excluded from the analysis to prevent severe model instability. Eighteen variables were fitted into the first model based on recommended significance criteria, with too few cases to control for variation among these exposures. The resultant wide confidence intervals calculated for some of the factors in the final multivariate model necessitate caution in the interpretation of the results.

5.4 Conclusions and Recommendations for Future Research

This research, while subject to limitations, has identified modifiable risk factors for invasive meningococcal disease. These include exposures previously identified, such as maternal smoking, humidity, attendance at bars, and an emergent risk factor, attendance at raves. Subject to replication in other studies, these findings could be used in the prevention of IMD in the community, such as smoking cessation programs targeting mothers (which is important for the prevention of IMD and other diseases), and promoting the use of humidifiers in the home. Rave and bar attendance will continue to be a reality among higher-risk age cohorts. However, subject to replication, the association identified with these exposures may be used in preventing the secondary spread of IMD. If not currently doing so, public health officials may consider collecting information on rave and bar attendance from all reported sporadic IMD cases, and subject to further confirmatory evidence, offer IMD prophylaxis to all individuals that patronized like facilities concurrently with the confirmed case.

The initiation of routine childhood immunization has greatly reduced the likelihood of future group C IMD outbreaks in Alberta. As discussed, outbreaks of IMD caused by serogroups not currently vaccine preventable (e.g. serogroup B) or not included in the current vaccine format (e.g. group Y) have recently been observed in North America. Public health agencies should consider IMD risk factors other than immunization status in the control of IMD.

Future community outbreaks of IMD should elicit the timely initiation of a similar case series description and risk factor study, which might also include the effectiveness of mass immunization campaigns when undertaken. A major limitation in this research was low statistical power and recall potential for exposures of interest, for which an important contributing factor was the time that had elapsed between the start of the outbreak and the recruitment of case participants. The study was initiated at the impetus of a University of Alberta student one year following the outbreak. While Capital Health is commended for sponsoring the research, initiating the study at the time of the outbreak may have improved the quality of the results. Research funding provided was sufficient only for the researcher to conduct the study on a part-time basis, which also contributed to the time required for participant recruitment, data collection and study completion. All public health agencies ought therefore to ensure that an adequate level of funding is continuously allocated for timely communicable disease outbreak prevention and management research, a move already recognized as being needed by Capital Health.

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Appendix A:

Review of key studies

Individual Review of Key Studies

A summary of each key study, from which modifiable risk factors measured for in this research were derived, follows. Unless otherwise stated, significant associations are those with an odds ratio point estimate above 1.0 and a 95% confidence interval entirely above 1.0. A list of key studies reviewed appears below:

Study 1: Stanwell-Smith RE. Stuart JM. Hughes AO. Robinson P. Griffin MB.Cartwright K. Smoking, the environment and meningococcal disease: a case control study. *Epidemiology & Infection*. 1994;112:315-28.

Study 2: Imrey PB. Jackson LA. Ludwinski PH. England AC 3rd. Fella GA. Fox BC. Isdale LB. Reeves MW. Wenger JD. Outbreak of serogroup C meningococcal disease associated with campus bar patronage. *American Journal of Epidemiology*. 1996;143:624-30.

Study 3: Fischer M. Hedberg K. Cardosi P. Plikaytis BD. Hoesly FC. Steingart KR. Bell TA. Fleming DW. Wenger JD. Perkins BA. Tobacco smoke as a risk factor for meningococcal disease. *Pediatric Infectious Disease Journal*. 1997;16:979-83.

Study 4: Kriz P. Bobak M. Kriz B. Parental smoking, socioeconomic factors, and risk of invasive meningococcal disease in children: a population based case-control study. *Archives of Disease in Childhood*. 2000;83:117-21.

Study 5: Baker M. McNicholas A. Garrett N. Jones N. Stewart J. Koberstein V. Lennon D. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. *Pediatric Infectious Disease Journal*. 2000;19:983-90.

Study 6: Robinson P. Taylor K. Nolan T. Risk-factors for meningococcal disease in Victoria, Australia, in 1997. *Epidemiology & Infection*. 2001;127:261-8.

Study 7: Bruce MG. Rosenstein NE. Capparella JM. Shutt KA. Perkins BA. Collins M. Risk factors for meningococcal disease in college students. *JAMA*. 2001;286:688-93.

Study 8: Cartwright KA. Jones DM. Smith AJ. Stuart JM. Kaczmarski EB. Palmer SR. Influenza A and meningococcal disease. *Lancet*. 1991;338:554-7

Study 9: Moodley JR. Coetzee. Hussey G. Risk factors for meningococcal disease in Cape Town. *South African Medical Journal*. 1999;89:56-59.

Study 10: Hodgson A. et al. Risk factors for meningococcal meningitis in northern Ghana. *Transactions of the Royal Society of Tropical Medicine & Hygiene*. 2001;95:477-80.

Study 11: Moore PS. Hierholzer J. DeWitt W. Gouan K. Djoré D. Lippeveld T. Plikaytis B. Broome CV. Respiratory viruses and Mycoplasma as cofactors for epidemic group A meningococcal meningitis. *JAMA* 1990;264:1271-75.

Study 12: Grein T. O'Flanagan D. Day-care and meningococcal disease in young children. *Epidemiology and Infection*. 2001;127:435-441.

Study 13: Pereiro I. Diez-Domingo J. Segarra L. Ballester A. Albert A. Morant A. Risk factors for invasive disease among children in Spain. *Journal of Infection*. 2004;48:320-9.

Study 14: Yusuf HR. Rochat RW. Baughman WS. Gargiullo PM. Perkins BA. Brantley MD. Stephens DS. Maternal cigarette smoking and invasive meningococcal disease: a cohort study among young children in metropolitan Atlanta, 1989-1996. *American Journal of Public Health*. 1999;89:712-7.

Study 15: Deutch S. Labouriau R. Schonheyeder HC. Ostergaard L. Norgard B. Sorensen HT. Crowding as a risk factor of meningococcal disease in Danish preschool children: a nationwide population-based case-control study.*Scandinavian Journal of Infectious Diseases*. 2004;36:20-3.

Study 16: McCall BJ, Neill AS, Young MM. Risk factors for invasive meningococcal disease in southern Queensland, 2000-2001. *Internal Medicine Journal* 2004;34:464-468.

Study 1: Stanwell-Smith RE. Stuart JM. Hughes AO. Robinson P. Griffin MB.Cartwright K. Smoking, the environment and meningococcal disease: a case control study. *Epidemiology & Infection*. 1994;112:315-28.

Design:	Matched case-control
Study population:	Eight health districts in west England
Case definition:	- positive culture in blood, CSF or tissue specimen, or - gram negative diplococci in CSF, or - positive culture in nasopharyngeal swab and/or rise in meningococcal antibodies in clinically diagnosed cases (with characteristic hemorrhagic rash)
Control group source:	population (GP registry)
Control of prognostic factors:	matching, adjustment (multivariate analysis)
Matching factors:	sex, age and registration with same family physician
Sample size:	74/74 (100%) eligible cases enrolled, 232 population-based controls (ratio of eligible not stated)
Data collection:	Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

All ages

- socio-economic status (1.89; 1.08-3.31)
- household crowding
  - >1 person/room (2.53; 1.16-5.55)
  - >1.5 persons/room (3.75; 1.01-14.0)
- 4 or more mouth kissing contacts (2.47; 1.27-4.83)
- nights away from home
  - all (2.23; 1.26-3.92)
  - within UK (2.46;1.37-4.43)
- any household smoker (1.84;1.04-3.26)
- exposure to ETS at home (2.13; 1.18-3.83)
- exposure to ETS on visits away from home (2.86;1.48-5.51)
- 2 smokers in household (1.91; 1.09-3.34)
- marital arguments (2.50; 1.20-5.20)
- other marriage difficulties (5.67; 1.39-23.2)
- indoor dust, all types (2.46; 1.44-4.20)
- holiday in last 6 months (0.35; 0.16-0.79)

≤5 years of age

- >6 persons in household (2.50; 1.14-5.48)
- >1.5 persons/room (6.00; 1.10-32.8)
- 4 or more mouth kissing contacts (2.46; 1.09-5.56)
- any household smoker (4.09; 1.59-10.70)
- exposure to ETS at home (4.67; 1.63-13.40)
- exposure to ETS on visits 3.00; 1.31-6.88)
- #cigarettes smoked in home/day
  - none (0.16; 0.03-0.85)
  - 10-19 (3.00; 1.19-7.56)
  - ≥30 (7.50; 1.46-38.7)
- smokers in household
  - none (0.13; 0.12-0.73)
  - 2 (2.53; 1.19-5.39)
- marital arguments (3.00; 1.26-7.17)
- change in living conditions (3.00; 1.09-8.25)
- holidays in last 6 months (0.24; 0.07-0.79)
- legal disputes (3.10; 1.24-7.78)
- indoor dust, all types (2.79; 1.35-5.76)

5 years of age and over

- 1.01-1.5 persons/room (4.75; 1.21-18.6)
- 2-3 mouth kissing contacts (3.17; 1.04-9.62)
- nights away from home
  - all (3.15; 1.40-7.12)
  - within UK (2.93; 1.29-6.62)
- other marriage difficulties (5.67; 1.39-23.4)

Study 2: Imrey PB. Jackson LA. Ludwinski PH. England AC 3rd. Fella GA. Fox BC. Isdale LB. Reeves MW. Wenger JD. Outbreak of serogroup C meningococcal disease associated with campus bar patronage. *American Journal of Epidemiology*. 1996;143:624-30.

Design:	Matched case-control
Study population:	Students at two U.S. colleges
Case definition: blood or CSF	- positive culture (or latex agglutination test) in
Control group source:	population (university telephone directory)
Control of prognostic factors:	matching, adjustment (multivariate analysis)
Matching factors:	college, sex, year in school
Sample size:	6/9 (67% of eligible) cases enrolled, 117 (86% of eligible) population-based controls
Data collection:	Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- cigarette smoking (7.8; 1.3-64.4)
- >4 hours in bar/week (16.7; 2.1-409.9)

Study 3: Fischer M. Hedberg K. Cardosi P. Plikaytis BD. Hoesly FC. Steingart KR. Bell TA. Fleming DW. Wenger JD. Perkins BA. Tobacco smoke as a risk factor for meningococcal disease. *Pediatric Infectious Disease Journal*. 1997;16:979-83.

Design: Matched case-control

Study population: States of Oregon, Washington (2 counties), U.S.A.

Case definition: positive culture in blood or CSF

Control group source: population (random digit dialing)

Control of prognostic factors: matching, adjustment (multivariate analysis)

Matching factors: age group, neighborhood (telephone number exchange)

Sample size: 129/140 (92%) eligible cases enrolled, 274 controls (90% of eligible)

Data collection: Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

≤18 years of age

- Mother smokes (3.8; 1.6-8.9)
- Maternal level of education (reference: college education
    - High school graduate (3.5; 1.1-10.8)
    - Not a high school graduate (6.5; 1.3-31.4)
- 3 or more children in home (2.5; 1.1-6.1)
- 30 or more children in school class (5.7; 1.3-24.2)
- Humidifier use (0.2; 0.1-0.9)
- Church attendance (0.2; 0.1-0.5)

18 years of age or more

- Chronic underlying illness (10.8; 2.7-43.3)

Study 4: Kriz P. Bobak M. Kriz B. Parental smoking, socioeconomic factors, and risk of invasive meningococcal disease in children: a population based case-control study. *Archives of Disease in Childhood*. 2000;83:117-21.

Design:	Matched case-control
Study population:	Those <15 years of age in Czech Republic (35 districts)
Case definition:	- positive culture in blood or CSF - antigen detection in CSF - direct microscopy of CSF - clinical signs only
Control group source:	population (schools attended by cases)
Control of prognostic factors:	matching, adjustment (multivariate analysis)
Matching factors:	age group, district, urban-rural place of residence
Sample size:	68 (96%) eligible cases enrolled, 135 controls from same school as case (percentage of eligible not stated)
Data collection:	Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- maternal smoking (3.52; 1.42-8.68)
- paternal smoking (3.21; 1.49-6.94)
- >20 cigarettes smoked in home daily (2.65; 1.31-5.35)

Study 5: Baker M. McNicholas A. Garrett N. Jones N. Stewart J. Koberstein V. Lennon D. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. *Pediatric Infectious Disease Journal*. 2000;19:983-90.

Design:	Matched case-control
Study population:	Those <8 years of age in Auckland, New Zealand
Case definition:	- positive culture in blood, CSF or other sterile site - positive PCR in blood or CSF - gram negative diplococci in blood or CSF
Control group source:	population (door-to-door cluster sampling)
Control of prognostic factors:	matching, adjustment (multivariate analysis)
Matching factors:	age group, ethnicity
Sample size: controls recruited	243/284 (86%) eligible cases enrolled; 313/374 (84%) eligible
Data collection:	Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- number of adults/adolescents in house/room (10.7; 3.9-29.5)
- analgesic use by child (proxy for URTI) (2.4; 1.5-4.0)
- number of days at substantial social gatherings (1.8; 1.2-2.6)
- number smokers in usual household 1.4 (1.0-1.8)
- respiratory infection in household member (1.5; 1.0-2.5)

Study 6: Robinson P. Taylor K. Nolan T. Risk-factors for meningococcal disease in Victoria, Australia, in 1997. *Epidemiology & Infection*. 2001;127:261-8.

Design: Matched case-control

Study population: Residents of Victoria, Australia

Case definition:

- positive culture from blood, CSF or other normally sterile site
- gram negative diplococci in normally sterile site
- probable clinical diagnosis

Control group source: population (convenience sampling by health practitioners and school administrators)

Control of prognostic factors: matching, adjustment (multivariate analysis)

Matching factors: age and sex, by neighborhood

Sample size: 87 (95%) eligible cases enrolled, 174 controls (92% of eligible)

Data collection: Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- smoker amongst intimate contacts (3.7; 1.9-7.5)
- contact with building/brush dust (2.9; 1.5-5.4)
- normally shares bedroom (2.7; 1.2-6.0)
- any illness in prior 2 weeks (3.3; 1.7-6.6)
- oral muscle tone deficiency (2.5; 1.2.4.9)

Study 7: Bruce MG. Rosenstein NE. Capparella JM. Shutt KA. Perkins BA. Collins M. Risk factors for meningococcal disease in college students. *JAMA*. 2001;286:688-93.

Design: Matched (nested) case-control

Study population: U.S. college students

Case definition:
- positive culture from normally sterile site
- positive antigen test, CSF
- probable clinical diagnosis

Control group source: population (college/universities attended by cases)

Control of prognostic factors: matching, adjustment (multivariate analysis)

Matching factors: college, sex, undergraduate vs. graduate status

Sample size: 50/75 (67%), eligible cases enrolled, 148/276 (54%) controls

Data collection: Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- Freshman living in college dormitory (3.6; 1.6-8.5)
- upper respiratory tract infection in month prior to onset (2.3; 1.0-5.3)
- White race (6.6; 1.2-38.0)
- Dwelling heated with radiator (4.0; 1.4-11.0)

Study 8: Cartwright KA. Jones DM. Smith AJ. Stuart JM. Kaczmarski EB. Palmer SR. Influenza A and meningococcal disease. *Lancet.* 1991;338:554-7

Design:	Matched case-control
Study population:	Those >10 years of age in England and Wales
Case definition:	positive culture
Control group source:	population (GP registry)
Control of prognostic factors:	matching
Matching factors:	age
Sample size: (convenience)	43 (81%) eligible cases had sera collected, 67 controls
Data collection:	Influenza serology

Significant association
(odds ratio; 95% confidence interval):

- serological evidence of recent influenza infection (3.9; 1.2-13.9)

Study 9: Moodley JR. Coetzee. Hussey G. Risk factors for meningococcal disease in Cape Town. *South African Medical Journal.* 1999;89:56-59.

Design:	Case-control
Study population:	Those <14 years of age in Cape Town, South Africa
Case definition:	- positive culture from blood or CSF - positive gram stain (CSF) and clinical signs - clinical signs
Control group source:	Hospital trauma wards
Control of prognostic factors:	adjustment (multivariate analysis)
Control eligibility:	>6 months in study population, hospital-recruited
Sample size:	70 cases, 210 controls (% eligible not stated)
Data collection:	Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- Breast fed <3 months (2.4; 1.3-4.4)
- Crowding (>2.5 persons/bedroom) (2.3; 1.0-5.3)
- interaction: recent upper respiratory tract infection URTI and passive exposure to ETS (3.6; 1.4-17.3)

Study 10: Hodgson A. et al. Risk factors for meningococcal meningitis in northern Ghana. *Transactions of the Royal Society of Tropical Medicine & Hygiene.* 2001;95:477-80.

Design:	Matched case-control study
Study population:	Geographic district in Northern Ghana
Case definition:	- sudden onset of fever and stiff neck - fever, stiff neck and altered mental status
Control group source:	population (neighborhood cluster sampling)
Control of prognostic factors:	matching, multivariate analysis
Matching factors:	age, sex, location (closest eligible control to case)
Sample size:	505 (91%) of eligible cases, 505 controls (proportion of eligible not stated)
Data collection:	Interviewer-administered questionnaire

Significant associations
(odds ratio; 95% confidence interval):

- sharing of bedroom with case (2.18; 1.43-3.4)
- cooking with firewood stove indoors (9.00; 1.25-395)

Study 11: Moore PS. Hierholzer J. DeWitt W. Gouan K. Djoré D. Lippeveld T. Plikaytis B. Broome CV. Respiratory viruses and Mycoplasma as cofactors for epidemic group A meningococcal meningitis. *JAMA* 1990;264:1271-75.

Design:	Matched case-control
Study population:	N'Djamena, Chad
Case definition:	fever, headache and positive CSF culture for serogroup A *N. meningitidis*
Control group source:	population (neighborhood cluster sampling)
Control of prognostic factors:	matching, multivariate analysis
Matching factors:	age, sex, neighborhood
Sample size:	62/73 (85%) of eligible cases, 62/65 (95%) eligible controls
Data collection:	nasopharyngeal washings, interviewer administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- Coincident upper respiratory tract infection (5.3; 1.7-16.1)

Study 12: Grein T. O'Flanagan D. Day-care and meningococcal disease in young children. *Epidemiology and Infection*. 2001;127:435-441.

Design:	Matched case-control
Study population:	Those <6 years of age, Eastern Regional Health Authority, Republic of Ireland
Case definition:	- positive culture from blood, CSF or other normally sterile site, or - clinical signs (petechial/purpuric lesions) - positive PCR test in blood, CSF or other normally sterile site, in those with clinical signs of meningitis or septicemia
Control group source:	population (child health registry)
Control of prognostic factors:	matching, multivariate analysis
Matching factors:	age, sex, socioeconomic class
Sample size:	87/130 (69%) of eligible cases, 261/390 (67%) eligible controls
Data collection:	(proxy) self-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- 5 or more adults in household (reference, 1-2) (5.4; 1.5-19.5)
- 2 or more household residents per bedroom (reference, <2) (1.8; 1.0-3.4)
- 3 or more smokers in household (reference, 0) (3.4; 1.3-9.1)
- daycare attendance (0.4; 0.2-0.9)

Study 13: Pereiro I. Diez-Domingo J. Segarra L. Ballester A. Albert A. Morant A. Risk factors for invasive disease among children in Spain. *Journal of Infection.* 2004;48:320-9.

Design:	Case-control (hospital based)
Study population:	Those <15 years of age, Valencia region, Spain
Case definition:	- positive culture from blood, CSF or other normally sterile site, or - clinical signs (hemorrhagic exanthema)
Control group source:	Hospitals at which cases admitted
Control of prognostic factors:	multivariate analysis
Sample size:	181 cases, (proportion of eligible not stated), 243 controls (proportion of eligible not stated)
Data collection:	interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- number of cigarettes smoked in home daily (reference, none)
    - 10-29 (2.35; 1.26-4.37)
    - 30-59 (1.01-4.34)
    - >59 (1.01-12.57)
- ≥4 household members (1.69; 1.01-2.85)

Study 14: Yusuf HR. Rochat RW. Baughman WS. Gargiullo PM. Perkins BA. Brantley MD. Stephens DS. Maternal cigarette smoking and invasive meningococcal disease: a cohort study among young children in metropolitan Atlanta, 1989-1996. *American Journal of Public Health.* 1999;89:712-7.

Design: Retrospective cohort

Study population: Those 3 years of age or less, Metropolitan Atlanta, U.S.A.

Case definition: positive culture from blood or CSF

Reference group source: Birth certificate database

Control of prognostic factors: multivariate analysis

Sample size: 47/49 (96%) of eligible cases, 283, 291 in study cohort

Data collection: Birth certificate database

Significant associations, multivariate analysis
(rate ratio; 95% confidence interval):

- pre-natal maternal smoking (2.9; 1.5-5.7)
- maternal education <12 years (2.1; 1.0-4.2)

Study 15: Deutch S. Labouriau R. Schonheyeder HC. Ostergaard L. Norgard B. Sorensen HT. Crowding as a risk factor of meningococcal disease in Danish preschool children: a nationwide population-based case-control study.*Scandinavian Journal of Infectious Diseases*. 2004;36:20-3.

Design:	Case-control (population based)
Study population:	Those <6 years of age in Denmark, 1980-1996
Case definition:	As per ICD-8 or ICD-10 for meningococcal disease
Control group source:	population (national registry)
Control of prognostic factors:	multivariate analysis
Sample size:	1222 cases, (proportion of eligible not stated), 24,549 controls (proportion of eligible not stated)
Data collection:	National registry database

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

- housing density (<20m^2/person, ref ≥50m^2/person)

- age <1 year (1.5; 1.1-1.9)
- age 1-5 years (1.5;1.1-2.0)

Study 16: McCall BJ, Neill AS, Young MM. Risk factors for invasive meningococcal disease in southern Queensland, 2000-2001. *Internal Medicine Journal* 2004;34:464-468.

Design:	Matched case-control (population based)
Study population:	Health region in Southwest Queensland, Australia
Case definition:	- positive culture from normally sterile site - gram negative diplococci in blood or CSF - detection of meningococcal antigen in joints, blood or CSF - detection of *N. meningitidis* nucleic acid in joints, blood, CSF, tissue or urine
Control group source:	medical practices (convenience sampling)
Matching factors:	age, medical practice
Control of prognostic factors:	matching, multivariate analysis
Sample size:	62/80 (78%) of eligible cases, 79 controls (proportion of eligible not stated)
Data collection:	Interviewer-administered questionnaire

Significant associations, multivariate analysis
(odds ratio; 95% confidence interval):

Under 6 years of age:

- sharing of a bedroom with 2 or more people (7.4; 1.5-36.1)
- primary carer that smoked (9.1; 2.1-39.9)

Appendix B:

First-stage recruitment script, case group participants

Informed consent script for initial contact. **Date:**______________
(of first attempt)

Case name: ______________________________________

Case phone number: ___________ Case age:_____(at first attempt)

Case NDR number: _______________ **Onset date:** _______________

Fatal Case? YES/NO **Consent received?Y/N/pending**

Contact attempt number (circle) **1 2 3 4 5**

Note: Roman numerals in the script pertain to the following case categories:

[I]	**case<18 years of age (at time of first contact), survivor**
[II]	**deceased case**
[III]	**case 18 years of age or older, (at time of first contact), survivor**

Please indicate category of case: **Category**_______________

Could I please speak with ________________________________

[If person of interest comes to telephone, skip to part B]

[If wrong number/person of interest doesn't live at residence anymore, skip to part C]

[If person of interest is not home]

Could you please have ________________________________ call me at 413-7927. I'll also try and call again later. Thank you. Goodbye.

[If non-English speaker]. Is there anyone there that speaks English? Could I speak with this person? [Skip to part B].

A. **[If answering machine].** I'm calling for ______________________

Hello, my name is *[name of Capital Health interviewer]* and I'm with Capital Health-Public Health Division, and I'm calling on behalf of the Medical Officer of Health. I'm calling to ask for participation in a research study about meningococcal meningitis. Could ____ please call me at 413-7927. I will also try and call again later. Thank you. Goodbye.

B. **[If person of interest comes to telephone]**

Hello, my name is *[name of Capital Health interviewer]* and I'm with Capital Health-Public Health Division, and I'm calling on behalf of the Medical Officer of Health. **[Continue to Part D]**

C. **[If wrong number/person of interest doesn't live at residence anymore]**

Would you be able to provide a phone number where I can reach ______
____

Record number if given: ______________________

Thank you. Goodbye.

D. **[If person of interest reached]**

I'm calling you at the request of a University of Alberta researcher who is doing a study about an infection called meningococcal meningitis, which is also called meningococcal disease.

Our records show that **you / your child / your spouse or loved one** were / was diagnosed with this infection during ________________ and so I'm calling to ask if you'd like to participate in the study. But before asking you, I'd like to tell you about the study, which will take approximately 3 – 4 minutes, OK?

The researcher, whose name is Lance Honish, is doing a study to try and find risk factors for meningococcal disease. The goal of the study is to help prevent others from getting this disease. To do this, the researcher is trying to get in touch with **people / parents or guardians of children / spouses or loved ones of people** who have had this infection since 1999 in the Edmonton area. If you agree to participate, he will call you in the next few weeks to give a questionnaire over the telephone.

The researcher will ask you to think back to the month before **you / your child / your spouse or loved one** got sick with meningococcal disease. These questions will be about things such as exposure to cigarette smoke, about time in crowded places, about your home, and some health-related questions, that might increase one's risk for getting meningococcal disease.

[FATAL CASES SKIP TO D2 on next page]

[If case is non-fatal and 12-17 years of age at time of phone call, continue].

The researcher will also ask your permission to ask some questions directly of your child, in private, without you being able to hear the questions he asks, or the answers your child gives. Questions that he'd like to ask your child in private are questions about cigarette smoking, and attendance at parties, clubs, bars, and so forth. So, for a part of the questionnaire, the researcher would ask your child to come to the telephone so that he can ask the questions directly to your child, without you listening to the questions or answers. The answers provided by your child would be kept confidential.

D2.

It may be that thinking back to the time that **you / your child / your spouse or loved one** got meningococcal disease is emotionally difficult for you. Remember that you do not have to participate in this study, and that you can refuse to participate at any time. Should you participate, you will also be provided the phone number of a Medical Officer of Health for Capital Health. You would be welcome to contact this individual if you have any further questions about meningococcal disease, information on how to obtain emotional counseling, if needed, and information on how to see results of the study.

Your name or any other identifying information will not be attached to the answers you give. Your name will also never be used in any presentations of the study results. Due to the small number of study participants, it cannot be guaranteed that all information you provide will remain completely anonymous, however, all information will be held confidential (or private), except when professional codes of ethics or legislation (or the law) requires reporting. The information you provide will be kept for at least five years after the study is done and will be kept in a locked filing cabinet at the offices of Capital Health. The information gathered for this study may be looked at again in the future to help us answer other study questions. If so, an ethics board will first review the study to ensure the information is used ethically.

Should you agree to participate, the researcher will contact you within the next few weeks, at a time that is convenient for you.

I'm calling you to ask your permission for two things. You have the right to not give your permission, for any reason. First, we're asking for your consent to allow Capital Health to tell the researcher that **you / your child / your spouse or loved one** had meningococcal disease. And second, we're asking for your consent for the researcher to call you by telephone, to give you the questionnaire I talked about. This questionnaire would take approximately 20 minutes.

If you have any questions about what's being asked of you, or about the research project, I can take them down and have a Medical Officer of Health call you. Do you have any questions?

[If question asked, record on back of page]. I will forward your question to a Medical Officer of Health, who will contact you with the answer. Are you comfortable with me continuing this phone call, or would you like the answer to your question first?

[If would like answer first]: I will forward your question to a Medical Officer of Health, and call you back in the next few days.

[If comfortable with continuing]: I will continue, but I will forward your question to a Medical Officer of Health your question and contact you with the answer in the next few days.

I am now going to ask for your consent to participate in the study, and instead of getting your consent in writing, I am going to tape record this part of our conversation. I'll tell you when I'm going to turn the tape recorder on and off.

Could you please state your first and last name?

Record name: ____

[If parent or guardian/spouse or loved one]

What is your relationship to____________________

[If parent or guardian/spouse or loved one]

Relationship to case: ___________________

OK, I'm turning on the tape recorder now. **[Turn on tape recorder]**

E. **Do you, ______________________________, give your consent for Capital Health to tell a University of Alberta researcher that you / your child / your spouse or loved one had meningococcal disease, and, do you consent to the researcher calling you about the study I talked about?**

Yes / No / refuses to answer / no answer

[If Yes] Today's date is ____________________. Thank you for participating.

[Turn off tape recorder] **I've now turned the tape recorder off.** **[Skip to E1]**

[If No/refused/no answer] Thank you for your time.

[Turn off tape recorder] **I've now turned off the tape recorder.** Goodbye.

E1 The researcher will contact you either during the day or evening. On what day and time do you suggest he call you?

Record the convenient time if given: ____________________

Do you have any questions before I let you go?

Thanks very much, goodbye.

Informed consent received? *(Y/N/pending)*

Date consent received: ____________________

Interviewer initials: __________

Interviewer comments/notes: ______________________________

____

____

Appendix C:

Follow-up letter for eligible participants not successfully contacted at first recruitment stage, case group participants

Appendix D:

Second-stage recruitment script, case/control group participants

Informed consent script. **Date:**______________
(of first attempt)

Case/control name: ________________________________
(followed by name of proxy, if applicable)

Case/Control #: ________________ **age at onset:**

*Case/control phone number:*________ *Age:* _____ _____

Onset date:____________________ **Case or Control**
(circle)

Consent received?Y/N/pending **Fatal Case? YES/NO**
(circle)

Contact attempt number (circle) **1 2 3 4 5**

[NOTE: If confusion is detected in a participant during the reading of the script, skip to [COGNATIVE DISABILITY SCRIPT] on page 9.

[NOTE: If lack of ability to communicate in English is detected in a participant during the reading of the script, skip to [NON-ENGLISH SCRIPT] on page 9.

A. [If telephone answered]

Hello, my name is Lance Honish, and I'm a graduate student at the University of Alberta.

Could I please talk to ____________________________
[name of person recruited by CHA/PRL].

[If person of interest (CASE) answers telephone, skip to part D]
[If person of interest (CONTROL) answers telephone, skip to part E]
[If person of interest comes to telephone after another answers, skip to part C]

Could you please have ______________________________________call me at 413-7923. I'll also try and call again later. Thank you. Goodbye.

B. [If answering machine].

Hello, my name is Lance Honish and I'm a graduate student at the University of Alberta, and I'm calling for __________________________

I'm calling to ask for participation in a research study about meningococcal disease that you were first called about on **[date of CHA/PRL contact].** Could ____________________________________please call me at 413-7923. I will also try and call again later. Thank you. Goodbye.

C. [If person of interest comes to telephone]

Hello, my name is Lance Honish and I'm a graduate student with the University of Alberta.

[CASES skip to Part D]
[CONTROLS skip to Part E]

D. [If person of interest (CASE) reached]

You were contacted on ______________________________
[date of contact by CHA]

by a representative of the Medical Officer of Health for Capital Health. During that phone call, you gave your permission for the Medical Officer of Health to tell me that **you / your child / your spouse or loved one** _____________
(name child/loved one)
had meningococcal disease in ______________________.
(month, date of onset)

You also you gave your permission to be contacted about participating in a research study about meningococcal disease.

Do you recall that phone call?

[SKIP TO PART F]

E. [If person of interest (CONTROL) reached]

You were contacted on ______________________________
[date of contact by PRL]

by the Population Research Laboratory at the Univerisity of Alberta. During that phone call, you gave your permission to be contacted about participating in a research study about meningococcal disease.

Do you recall that phone call?

F. Continue reading script below

I'm calling now to ask your permission to participate in the study, and, if you agree to participate, I'll ask you some questions **about your child (state name of child)/ about your spouse or loved one** in a survey that will take about 15 to 20 minutes to complete. Are you able to talk about this right now?

[If no]. When would be a better time for me to call?

____

(record time if given)
Thank you. I will call back then. Goodbye.

Thank you. I'd now like to briefly tell you about the study, and then, I need to ask for your permission to participate in the study. Just to refresh your memory, the study is looking at risk factors for an infection called meningococcal disease in the Capital Health region. You may remember the outbreak of this infection between 1999 and 2002 in the Edmonton area, when over 80 people got sick with this illness and over 250,000 people were immunized. We're asking questions of people who got sick with this infection in the Edmonton area between 1999 and 2002, and of people who didn't get the infection, to see we can find any factors that may increase people's risk of getting meningococcal disease. These questions will be about things that might increase one's risk for getting meningococcal disease, such as exposure to cigarette smoke, about time in crowded places, about your home, and some health-related questions. The goal is to help prevent this illness in the future.

[If participant is <12 years of age at time of phone call, skip to Part G].

[If participant is 18 years of age or older at time of phone call, skip to Part G].

I will also ask your permission, and your child's permission, to ask some questions directly of your child, in private, without you being able to hear the questions I ask, nor the answers your child gives. Questions that I'd like to ask your child in private are questions about cigarette smoking, and attendance at parties, clubs, bars, and so forth. So, for a part of the questionnaire, I will ask your child to come to the telephone so that I can ask the questions directly to your child, without you listening to the questions or answers. The answers provided by your child would be kept confidential.

G. [CONTROLS skip to Part H]

It may be that thinking back to the time that **you / your child / your spouse or loved one** got meningococcal disease is emotionally difficult for you. Remember that you do not have to participate in this study, and that you can refuse to participate at any time. Should you participate, you will also be provided the phone numbers of people to contact if you have any further questions about meningococcal disease, information on how to obtain emotional counseling, if needed, and information on how to see results of the study.

H. Continue reading script below

Remember that you do not have to participate in this study, and that you can refuse to participate at any time. Should you participate, you will also be provided the phone numbers of people to contact if you have any further questions about meningococcal disease and information on how to see results of the study.

I'll now tell you how the information you provide will be kept confidential, or private.

Your name or any other identifying information will not be attached to the answers you give. Your name will also never be used in any presentations of the study results. Due to the small number of study participants, it cannot be guaranteed that all information you provide will remain completely anonymous, however, all information will be held confidential (or private), except when professional codes of ethics or legislation (or the law) requires reporting. The information you provide will be kept for at least five years after the study is done and will be kept in a locked filing cabinet at the offices of Capital Health. The information gathered for this study may be looked at again in the future to help us answer other study questions. If so, an ethics board will first review the study to ensure the information is used ethically.

Do you understand what I'm asking of you? Do you have any questions of me before we continue?

I am now going to ask for your consent to participate in the study, and instead of getting your consent in writing, I am going to tape record a part of our conversation. I'll tell you when I'm going to turn the tape recorder on and when I've turned it off.

Could you please state your first and last name?

Record name: ____

[If parent or guardian/spouse or loved one]

What is your relationship to ________________

[If parent or guardian/spouse or loved one]

Relationship to case: ______________________

OK, I'm turning on the tape recorder now. **[Turn on tape recorder]**

I. **Do you, ____________________________________, give your consent to participate in this University of Alberta study about meningococcal disease, in which you will answer questions**

[about your child ________________________
(state name of case)

[about your spouse or loved one ________________________
(state name of case)

over the telephone in a survey?

Yes / No / refuses to answer / no answer

[If Yes] Today's date is ______________________. Thank you for participating.

[Turn off tape recorder] **I've now turned the tape recorder off.**

[If Consent received and Cases/control is >12 and <18 years old, skip to Part J]

[If No/refused/no answer] Thank you for your time.

[Turn off tape recorder] **I've now turned off the tape recorder, and we can proceed to the survey.**

Informed consent received? (Y/N/pending)

Date consent received: ____________________

Interviewer initials: ____________________

Interviewer comments/notes: ____________________

[Proceed to questionnaire start]

J. [Parents of case/control >12 and <18 years old].

Before starting the questionnaire, I also require your child's consent to answer questions of him or her. It would be best if both you and your child were home at the same time. Is your child at home right now? [If no] Is there a time that I could call when both of you would be at home?

____

(record time if given)

Could you please put your child on the telephone so I can get his/her consent as well?

Hi, this is [name of case]?

Hello, I'm Lance Honish, a student with the University of Alberta. I'm doing a study about a disease called meningococcal meningitis. The study will try and find things that put people at more risk for the disease. By finding out what these things are, we can maybe prevent other people from getting the disease. [Cases] Your parent told me that you had meningococcal disease in [month, year of case onset]. I'm calling people your age to ask some questions over the telephone. I would first ask your parent some questions about you, and then I would ask you some questions. Your parent said it would be OK if I asked you some questions, but you're a mature person, and so it's important that I ask for your permission, too. The questions I would ask of you would be asked in private, so that your parent can not hear the questions or the answers. I will not tell your parent your answers to my questions. You do not have to give me your permission, and if you do not give your permission, no one will be angry with you. All of the answers you give will be kept private. You have the right to not answer any question I ask, and you have the right to end this phone call at any time.

Do you understand what I'm asking of you? Do you have any questions of me?

I need to tape record your permission, so I'm going to turn on a tape recorder now and record this next question. I will turn the tape recorder off after you have answered this question.

Do you, [name of 12-17 year old participant] give your permission to participate in this University of Alberta study about meningococcal meningitis, in which you will answer questions over the telephone in a survey?

__________ **Yes** __________ **No**

Today's date is [state date]. I'm turning off the tape recorder now.

Could I please talk to your parent again?

Thank you. Do you have any questions before we begin?

Informed consent received? *(Y/N/pending)*

Date consent received: ____________________

Interviewer initials: ___________

Interviewer comments/notes: ____________________________
____
____
____
____
____
____
__

[Proceed to questionnaire start]

[COGNATIVE DISABILITY SCRIPT] Could I please talk to your parent or another loved one at home? [If no one available: could you let me know when someone else in your household might be available?]. [If suitable proxy respondent comes to the telephone]. Hello, my name is Lance Honish, and I'm a graduate student at the University of Alberta. I'm looking at factors that may increase the risk for an infection called meningococcal disease in the Capital Health region. You may remember the outbreak of this infection between 1999 and 2002 in the Edmonton area, when over 80 people got sick with this illness and over 250,000 people were immunized. We're asking questions about people who got sick with this infection between 1999 and 2002, and about people who didn't get the infection, to see if we can find any factors that may increase people's risk of getting meningococcal meningitis. The goal is to help prevent this illness in the future. The survey involves a 20-minute questionnaire over the telephone. While I was speaking with [name of potential participant] I detected that they might be unsure about just what I was asking of them. Do you feel that [name of participant] is able to understand that I am asking them to participate in a research study, and they have the choice of not participating if they so choose? [If yes]. Thank you. Could you please ask [name of participant] to come back to the phone? [If no]. Might you be willing to participate on their behalf? [If Yes, skip back to part B]. [If no]. Thank you for your time. Goodbye.

[?NON-ENGLISH SCRIPT] Could I please talk to your parent or another loved one at home? [If no one available: could you let me know when someone else in your household might be available?]. [If suitable proxy respondent comes to the telephone]. Hello, my name is Lance Honish, and I'm a graduate student at the University of Alberta. I'm looking at factors that may increase the risk for an infection called meningococcal disease in the Capital Health region. You may remember the outbreak of this infection between 1999 and 2002 in the Edmonton area, when over 80 people got sick with this illness and over 250,000 people were immunized. We're asking questions about people who got sick with this infection between 1999 and 2002, and about people who didn't get the infection, to see if we can find any factors that may increase people's risk of getting meningococcal meningitis. The goal is to help prevent this illness in the future. The survey involves a 20-minute questionnaire over the telephone. While I was speaking with [name of potential participant] I detected that they might be able to understand what I was asking of them because they have trouble communicating in English. Do you feel that [name of participant] is able to understand in English that I am asking them to participate in a research study? [If yes]. Thank you. Could you please ask [name of participant] to come back to the phone? [If no]. Might you be willing to participate on their behalf? [If Yes, skip back to part B]. [If no]. Thank you for your time. Goodbye.

Appendix E:

Follow-up letter for eligible participants not successfully contacted at second recruitment stage, case group participants

January 21, 2004

(insert address)

Dear ____________________:

Re: **Meningococcal disease research study**
Request for participation

I write to you on behalf of a University of Alberta researcher, who is seeking people such as yourself to participate in a study about meningococcal disease. You may remember the outbreak of this infection between 1999 and 2002 in the Edmonton area, when over 80 people got sick with this illness and over 250,000 people were immunized.

This office contacted you by telephone on __________ 2003, when you provided consent to be contacted by the researcher about participating in the study. However, your phone number has apparently changed since that time, which is why you have received this letter.

The researcher (Lance Honish) is conducting a study to try and find risk factors for meningococcal disease. The goal of the study is to help prevent others from getting this disease. To do this, the researcher is trying to get in touch with *[people / parents or guardians of children / spouses or loved ones of people]* who have had this infection since 1999 in the Edmonton area, to ask them questions in a survey over the telephone that would take approximately 20 minutes.

Your participation would be valued and greatly appreciated by the researcher.

If you are interested in participating in the study, **please call Capital Health at (780) 413-7923** at your earliest convenience.

Sincerely,

Gerry Predy MD FRCPC
Medical Officer of Health

Appendix F:

Summary of first stage control participant recruitment, Population Research Laboratory, University of Alberta

RISK FACTORS FOR
INVASIVE MENINGOCOCCAL DISEASE
EDMONTON, ALBERTA, 1999 – 2002
A CASE CONTROL STUDY

Summary of Data Collection Statistics

Prepared for

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and
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Department of Public Health Sciences
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by the

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August 18, 2004

Dr. Colin Soskolne of the Department of Public Health Sciences, Faculty of Medicine and Dentistry at the University of Alberta, contracted the Population Research Laboratory (PRL) to recruit people in the Capital Health region (pre April 1, 2003 boundaries) for participation in a case-control study for invasive meningococcal disease. In a case-control study, people who have developed the disease are identified and their past exposure to suspected factors are compared with those who do not have the disease. The primary objective of this study is to determine whether there are any significant modifiable risk factors that may increase or decrease a person's risk of contracting meningococcal disease.

In this study 50 people who had developed the meningococcal disease were identified. Two controls per case were needed to be recruited from the general population. A total of 101 controls were recruited for this study. Table 1 shows the quota of controls by gender and age. Only one control per household was permitted. The controls were matched with the case on gender and age and met the following criteria: 1) living in the Edmonton area all the time since 1999; 2) never contracted meningococcal meningitis; and 3) never contracted meningococcemia.

Children that were between 0 to 24 months at the onset of meningococcal disease outbreak were treated differently. Beside gender, the controls must also be matched with the case at onset within the same dates of birth range (not a particular age in years) (Table 2). The reason was that the matched control would be asked about exposures that took place in the month before the matched case's onset. All other controls would be matched by age in years of the cases based on their age on November 1, 2003.

The recruitment took place in two phases. The first group of controls to be recruited were those aged 18 and over. This age group constituted two-thirds of the control population. Then, it was followed by the recruitment of the remaining one-third - children under the age of 18. This strategy of recruitment was directed at the latter group, where informed consent from parent or guardian was required. The telephone script was modified to reflect this recruitment guideline. As well, it enabled the interviewers to concentrate on one group of control at a time.

TABLE 1: Quota of Controls by Gender and Age

	Gender	
Age	***Male***	***Female***
3 **	4	2
4 **	4	4
6	0	4
8	2	0
9	2	0
11	2	0
12	2	0
14	2	2
16	2	2
17	0	2
18	2	0
20	4	6
21	4	4
22	8	4
23	0	2
24	2	0
26	2	2
31	0	2
36	2	2
39	2	0
46	0	2
47	2	0
51	0	4
63	0	2
67	2	0
78	0	2
81	2	0
Total	**52**	**48**

** Please reference Table 2 for the range of dates of birth that the matched controls needed to fall within.

TABLE 2: Range of Dates of Birth of Matched Controls

Age of Matched Controls	*Age of Case at Onset*	*Range of Dates of Birth*
3	0 - 6 months	July 28, 2000 – January 28, 2001
3	6 - 12 months	September 6, 1999 – March 6, 2000 January 12, 2000 – July 12, 2000
4	0 – 6 months	July 7, 1999 – January 7, 2000
4	12 – 24 months	July 24, 1998 – July 24, 1999 November 29, 1998 – November 29, 1999 December 27, 1998 – December 27, 1999

Prior to administering the study, the recruitment instrument was reviewed and approved by the Health Research Ethics Board (HREB). The HREB is a joint committee of the University of Alberta Health Sciences Faculties, the Capital Health Authority, and the Caritas Health Group.

At the outset of the study, the telephone interviewers and supervisors received training from the Research Coordinator and the researcher, Mr. Lance Honish, on the study background, content of the recruitment instrument and ethical considerations.
The PRL worked with the researcher to develop the telephone recruitment script for the target age strata. The instrument was then formatted electronically for the main data collection phase. The PRL conducted data collection from centralized Computer-Assisted Telephone Interviewing (CATI[1]) facilities at the University of Alberta.

Prior to data collection, the PRL generated a telephone sample for the study and loaded it into the CATI system. A random digit dialing approach was used to ensure that respondents had an equal chance of being contacted whether or not their household was listed in the telephone survey. The sample contained telephone numbers for the entire Capital Health region.

Interviewing for the main study took place between October 21, 2003 and November 25, 2003. Callbacks and interviews were scheduled from 9:30 a.m. to 2:30 p.m. and 4:00 p.m. to 9:00 p.m. Monday to Friday, 10:00 a.m. to 4:00 p.m. on Saturdays, and 2:00 p.m. to 8:00 p.m. on Sundays. For each telephone number, up to 10 call attempts were made on various days and at different times of day in order to increase the possibility of contact with eligible households. Telephone supervisors monitored the work of the interviewers, checked call dispositions, and conducted back-up interviewing.

Before administering the recruitment questions, the respondents were informed by the interviewers that their participation was voluntary and information they gave to the research study would be kept confidential. Respondents had the right to terminate the interview at any time. The respondents were also assured that their interview was protected under the Alberta Freedom of Information and Protection of Privacy Act (FOIPP) and would only be used for research purposes.

When recruiting controls under the age of 18, interviewers were instructed to speak to the parent or guardian for their permission to recruit their child. In addition, for recruiting children between the ages of 12-17, the researcher also required the consent to speak with the youth in private questions about their lifestyle. Youth of this age group sometimes take part in activities that might put them at higher risk of meningococcal disease. The answers provided by the youth would be kept confidential.

---

[1] The Ci3 WINCATI System is a PC based product of Sawtooth Software, Northbrook Illinois.

The final call dispositions for the total sample are shown in Table 3. Reasons given for refusal to be recruited included: not interested, no time, would not give out information over the phone, hung up, etc. In some instances, respondents simply did not stay on the phone long enough to hear the introduction of the study. The *Permanent No Contact* category included respondents away during recruitment period or very difficult to reach (e.g., traveling out of town, personal commitments and obligations).

TABLE 3: CATI Dispositions – Final Outcome of Call Attempts

CATI Dispositions Final Outcome of Call Attempts	Frequency	% of Records
No Answer	480	7.3
Busy	53	0.8
Answering Machine	1,004	15.3
Recruits	101	1.5
Line Trouble	159	2.4
Call Back	32	0.5
Initial Refusal	765	11.6
Language Barrier	59	0.9
Not in Service	1,027	15.6
Business/Fax	1,275	19.4
Permanent No Contact	7	0.1
Ineligible –Quota Full/Age Outside Quota Range	1,525	23.2
Ineligible – Not Lived in Edmonton (all the time) Since 1999	63	1.0
Ineligible – Had Meningococcal Meningitis	1	0.0
Ineligible – Had Meningococcemia	0	0.0
Family Crisis/Illness	19	0.3
Will Call Lab	1	0.0
Total	**6,571**	**100**

Table 4 shows the breakdown of the number of call attempts for the final disposition of recruits (n=101) and all call records (n=6571). On average, a recruit took two call attempts. The average interview time was 4.5 minutes for a recruit. A total of 13963 telephone calls were needed to recruit 101 case controls for this study.

TABLE 4: Number of Call Attempts for Recruits and for All Call Records

	Recruits			*All Call Records*		
Number of Attempts	**Frequency**	**Percent**	**Cumulative Percent**	**Frequency**	**Percent**	**Cumulative Percent**
1	35	34.7	34.7	3,382	51.5	51.5
2	24	23.8	58.4	1,140	17.3	68.8
3	18	17.8	76.2	715	10.9	79.7
4	17	16.8	93.1	711	10.8	90.5
5	4	4.0	97.0	513	7.8	98.3
6	1	1.0	98.0	64	1.0	99.3
7	1	1.0	99.0	23	0.4	99.6
8	0	0.0	99.0	10	0.2	99.8
9	0	0.0	99.0	8	0.1	99.9
10	1	1.0	100.0	5	0.1	100.0
Total	**101**	**100.0**	**100.0**	**6,571**	**100.0**	**100.0**

Upon completion of the recruitment interviews, a diskette containing name and telephone number of recruits was provided to the researcher to administer the next phase of this study. During this phase, interviewing of controls was conducted by the researcher. The same standardized questionnaire used for the cases was administered to the controls. Information sought included factors that might increase one's risk for getting meningococcal disease, such as exposure to cigarette smoke, about time in crowded places, home environment, and some health-related items.

In accordance with ethical guidelines for the conduct of research, case controls were free to withdraw their consent and discontinue participation at any time. The controls lost during the follow-up interview phase were replaced through additional recruitment. Wave 2 of control recruitment was conducted from June 3, 2004 to June 29, 2004 to replace the 26 cases of initial controls lost to follow-up interview. Age match was based on the control's age as of June 1, 2004. Table 5 profiles the 26 cases of lost controls by gender and age. The last wave of control recruitment (Wave 3) commenced on July 19, 2004 to recruit a 81 years old male, a 22 years old male and a 22 years old female. The entire recruitment process of controls was completed on July 30, 2004. In contrast to Wave 1, interviewers contacted and screened a significantly larger number of call records in Wave 2 and Wave 3 in order to determine their eligibility requirements and to obtain their informed consent to participate. A total of 3811 telephone numbers was used.

TABLE 5: Wave 2 Quota of Controls by Gender and Age

	Gender	
Age	**Male**	**Female**
4	0	1
6	0	1
9	1	0
13	1	0
15	0	1
17	1	0
18	0	1
21	0	3
22	4	2
36	2	0
37	0	1
48	1	0
52	0	2
63	0	2
67	1	0
81	1	0
Total	**12**	**14**

TABLE 1

Wave 2 and Wave 3
CATI Dispositions – Final Outcome of Call Attempts

CATI Dispositions Final Outcome of Call Attempts	Frequency	% of Records
No Answer	360	9.4
Busy	28	0.7
Answering Machine	597	15.7
Recruits	29	0.8
Line Trouble	58	1.5
Call Back	27	0.7
Initial Refusal	298	7.8
Language Barrier	21	0.6
Not in Service	572	15.0
Business/Fax	753	19.7
Permanent No Contact	8	0.2
Ineligible –Quota Full/Age Outside Quota Range	1,040	27.3
Ineligible – Not Lived in Edmonton (all the time) Since 1999	15	0.4
Ineligible – Had Meningococcal Meningitis	0	0
Ineligible – Had Meningococcemia	0	0
Family Crisis/Illness	3	0.1
Will Call Lab	2	0.1
Total	**3,811**	**100**

Table 2 shows the breakdown of the number of call attempts for the final disposition of recruits (n=29) and all call records (n=3811). On average, a recruit took two call attempts. The average interview time was 6.1 minutes for a recruit. A total of 6587 telephone calls were needed to recruit 29 case controls for this study.

TABLE 2

Wave 2 and Wave 3
Number of Call Attempts for Recruits and for All Call Records

	Recruits			***All Call Records***		
Number of Attempts	**Frequency**	**Percent**	**Cumulative Percent**	**Frequency**	**Percent**	**Cumulative Percent**
1	16	55.2	55.2	2,136	56.0	56.0
2	9	31.0	86.2	811	21.3	77.3
3	2	6.9	93.1	704	18.5	95.8
4	0	0	93.1	122	3.2	99.0
5	2	6.9	**100.0**	26	0.7	99.7
6	0	0		3	0.1	99.8
7	0	0		7	0.2	**100.0**
8	0	0		0	0	**100.0**
9	0	0		0	0	**100.0**
10	0	0		1	0	**100.0**
11	0	0		0	0	**100.0**
12	0	0		1	0	**100.0**
Total	**29**	**100.0**	**100.0**	**3,811**	**100.0**	

Appendix G:

Letter to case participants regarding halting of Quebec invasive meningococcal disease study

October 20, 2004

[Name and address of participant (case or proxy)]

Dear [name of case or proxy]:

On [date of questionnaire administration], you were contacted by Lance Honish, a graduate student at the University of Alberta, who asked you to complete a survey about meningococcal disease over the telephone. At the end of the interview, he asked for your mailing address, for two reasons: 1) so that the telephone number of someone to contact for more information about the University of Alberta study could be mailed to you, and 2) so that information could be sent to you about another meningococcal disease study, which was being carried out by the Centre Hospitalier Universitaire De Sherbrooke, Quebec. This information is provided below.

1) Telephone number of someone to contact about the University of Alberta study that Lance Honish, graduate student, called you about on [date of questionnaire admin]:

   For further information about the University of Alberta study, or for information on how to obtain the results of the University of Alberta study when they are available in approximately 6 months, please contact Dr. Colin Soskolne, Department of Public Health Sciences, Faculty of Medicine and Dentistry, University of Alberta, at (780) 492-6013.

2) The meningococcal disease study being carried out by the Centre Hospitalier Universitaire De Sherbrooke, Quebec, has been stopped. Therefore, your participation is not required at this time.

Should you have any further questions, please contact me at (780) 413-7601.

Thank you for your participation in the study.

Sincerely,

Marcia M Johnson MD FRCPC
Deputy Medical Officer of Health

Appendix H:

Data collection instrument template

Qtre # ______ ("A"-case, "B"-control 1, "C"-control 2)

Date of Case onset (month, year)____________________________

Deceased Case? ____________ Age: _____ age at onset: ________

Date: ________________ Time elapsed since onset: ________ (years)

Note 1: Questions will be asked about "your child" for cases <18 (fatal or survivors), and about "your spouse or loved one" for deceased cases 18 years of age or older.

For controls, "[month and year of case onset]" refers to the month and year before onset of IMD in the case to which the control has been matched by age.

Note2: ***DK="Don't know" NS="Not sure"***

[If case becomes noticeably emotionally upset during the interview, skip to UPSET SCRIPT on page #26]

Many of my questions ask that you please think back in time [time elapsed since case onset], to [cases: the month before you got sick, in] [month, year of case onset]. Now it may be difficult for you to remember specific details from that time, so I am looking only for your best recollection in your responses to my questions.

[<5 year-old child case] Some question will ask about "shots" or vaccinations your child has had, and it might be helpful to have your child's immunization record card available. Do you know where it is? Could I give you a moment to find it and return to the telephone?

Travel

Question 1 script: I'm going to start by asking you some questions about your_ residence in Canada, and your_ travel history.

[canlife]

1. Have_you lived in Canada for all of your_ life?

________	______	_____	_____	__________
Yes	No	DK	NS	refused

[If YES, skip to question 1c below]

[yearcan]

1. b. What was the last year that you_ did not live in Canada? *CODE:*

______ (record year) ______ DK ______ refused ______ *(how long In Canada Before onset)*

[overcan]

1. c. Did_you stay overnight in a place away from home, within Canada in [cases: the month before you got sick, in] [month, year of case onset]?

______ Yes ______ No ______ DK ______ NS ______ refused

2. Did_you travel outside of Canada during [year of case onset]?

______ Yes ______ No ______ DK ______ NS ______ refused

[If no/DK/refused, skip to script for question 3 below]

[travint]

2. a. Were_you outside of Canada during [cases: the month before you got sick, in] [month, year of case onset]?

______ Yes ______ No ______ DK ______ NS ______ refused

Question 3 Script: I'm now going to ask you SOME questions about snoring and about speech.

3. Do_you usually snore while you_ sleep_ ?

______ Yes ______ No ______ DK ______ NS ______ refused

[If no/DK/refused, skip to question 4 below]

[snore]

3. a. Had you known about your_ snoring before [cases: the month before you got sick, in] [month, year of case onset]?

______ Yes ______ No ______ DK ______ NS ______ refused

4. Have_you ever been referred to a speech therapist because you_have trouble speaking?

______ Yes	______ No	______ DK	______ NS	______ refused

[DECEASED cases skip to DECEASED script for question 5 below]

[If no/DK/refused, skip to non-deceased script question 5 below]

[speech]

4. a Were_you referred to the speech therapist before
[cases: the month before you got sick, in] [month, year of case onset]?

______ Yes	______ No	______ DK	______ NS	______ refused

Household DENSITY (all)

Question 5 NON-deceased script: I'm now going to ask you some questions about the home you_ live_ in now, and the home you_ lived in [time elapsed since case onset] ago, during [cases: the month before you got sick, in] [month, year of case onset].

Question 5 DECEASED script: I'm now going to ask you some questions about the home you~ lived in [time elapsed since case onset] ago, during
[cases: the month before you got sick, in] [month, year of case onset].

[DECEASED CASES SKIP TO QUESTION 7 BELOW]

5. How long, in months or years, have_you lived at your_ current address?

______YRS__________MOS Record length of time	______ DK	______ NS	______ refused

[If length given shorter than [time elapsed since case onset], skip to script at the end of question 6 below]

6. So, were_you living at your current address during
[cases: the month before you got sick, in] [month, year of case onset]?

______ Yes	______ No	______ DK	______ NS	______ refused

[If Yes, skip to question 7 below]

SCRIPT: I now would like you to think back to the home that `you were` living in during [cases: the month before you got sick, in] [month, year of case onset]

[#bedroom]

7. How many bedrooms were there in your_ home in [cases: the month before you got sick, in] [month, year of case onset]?

____
(number of bedrooms—DK/refused/not sure, enter "D", "R", "N", respectively

[resnum]
[density]

8. Including yourself_, how many people lived in your_ home in [cases: the month before you got sick, in] [month, year of case onset]?

____ *Code: Density*______________

(number of people—DK/refused/not sure, "D", "R", "N", respectively)

[If answer "1", skip to question 10 below]

[res10]

9. How many people that lived in your_ home in [cases: the month before you got sick, in] [month, year of case onset] were less than 10 years old at that time? (DK/refuse /not sure, enter "D", "R", "N", respectively, for both)

____	______	______________
(number aged <10)	*Code: (number 10 or older)*	*Code: total*

[otbedrm]

10. In [cases: the month before you got sick, in] [month, year of case onset], did anyone other than you_ regularly sleep in your_ bedroom?

________	________	________	______	________
Yes	No	DK	NS	refused

[If no/DK/refused, record "1" in question 11 below, and skip to question 12 below]

[otbednum]

11. How many people, including yourself_, would regularly sleep in your_ bedroom during [cases: the month before you got sick, in] [month, year of case onset]?

__________ record # of people   ________ DK   ______ NS   __________ refused

[furnace]
[radiat]
[wood]
[heatoth]

12. What type of heating was there in your_ home during [cases: the month before you got sick, in] [month, year of case onset]? Please choose from the following types:

a. Furnace Y____ N____ NS___ DK_______ refused_____
b. Radiator heating pipes Y____ N____ NS___ DK_______ refused_____
c. Wood Y____ N____ NS___ DK_______ refused_____
d. Other Y____ N____ NS___ DK_______ refused_____

[Response other than furnace, skip to script for question 13 below]

[furnhum]

13. a. Did the furnace have a humidifier attached to it in [cases: the month before you got sick, in] [month, year of case onset]?

________ Yes   ________ No   ______ DK   _____ NS   _________ refused

[humoth]

13. b. Was a humidifier sometimes used in the home you_ lived in during [cases: the month before you got sick, in] [month, year of case onset], one that was not attached to a furnace?

________ Yes   ________ No   ________ DK   _____ NS   _________ refused

[firepl]

14. Did the home you_ lived in during [cases: the month before you got sick, in] [month, year of case onset] have a fireplace in which real wood is used?

________ Yes   ________ No   ________ DK   ______ NS   __________ refused

Household dust/particulates

15. At any time during [year of case onset] was your_ home being renovated inside that made the home more dusty than usual?

________	________	________	________	________
Yes	No	DK	NS	refused

[If no/DK/refused, skip to question 16 below]

[renos]

15. b. Were these renovations happening during
[cases: the month before you got sick, in] [month, year of case onset]?

________	________	________	________	________
Yes	No	DK	NS	refused

[Controls skip to script for question 18 below]

<u>Antecedent illness</u>

Script for question 16: I'm now going to ask some questions about any illness with a cough.

[cough]

16. In [cases: the month before you got sick, in] [month, year of case onset] were_you sick with a cough?

________	________	________	________	________
Yes	No	DK	NS	refused

[If no/DK/refused, skip to script for question 18 below]

[newcough]

17. a. Was this cough a new cough, which was different FROM a cough you_ might normally_have?

________	________	________	________	________
Yes	No	DK	NS	refused

[If no/DK/NS/refused, skip to script for question 18 below]

[fevcough]

b. While `you were` sick with this cough, did you_ have a fever?

________	________	________	________	________
Yes	No	DK	NS	refused

Immunization (all)

Script for question 18: I'm now going to ask you some questions about vaccinations or "shots" you_have had. You might remember, in 2000_ and 2001_, everyone aged 2 to 24 in the Edmonton area was offered the meningococcal meningitis "shot" to protect them from this infection, at clinics throughout the area. In addition, people sometimes get this shot if they travel to an area with a lot of meningococcal meningitis

[child cases <5 years old only] and infants born after July 2001 are offered the shot as part of routine immunizations.

[immever]

18. a. Did you_ ever receive the meningococcal meningitis shot?

_________	_________	_________	______	_________
Yes	No	DK	NS	refused

[If Yes and [age at onset] is older than 1 year, skip to question 18 e below]

[If no and [cases: the month before you got sick, in] [month, year of case onset] is before Feb 2000, skip to question 20]

[If no and [age at onset] is 24 years or less skip to question 19 below]

[If no and [age at onset] is more than 24 years skip to question 20 below]

[If DK/NS/refused, skip to question 20 below]

b. Children who are younger than 12 months of age when vaccinated require more than one meningococcal shot. About how old, in months or years, was your child at the time the meningococcal shot was first given? If you're able, it might be helpful to check your child's immunization card to answer this question.

____
(record age)

c. How many meningococcal shots did your child receive? Again, if you're able, it might be helpful to check on your child's immunization card to answer this question.

Code:

_______________	_________
(record number)	*(immunized?)*

[immpart]

d. Did your child receive the all of the meningococcal shots before [cases: the month before you got sick, in] [month, year of case onset]?

Yes   No   DK   NS   refused

[skip to script for question 20 below]

[immprot]

e. Did you_ receive the shot before [cases: you got sick? I remind you that you got sick in] [month, year of case onset]?

Yes   No   DK   NS   refused

[skip to script for question 20 below]

[immreas]

19. What was the main reason, would you say, that you_ didn't get the meningococcal meningitis shot? Please choose from the following options:

Couldn't get to clinics ________
Lineup too long ________
Scared of needles ________
Didn't think it was necessary ________
Didn't know about immunization campaign ________
Other (specify): ________________________________
DK ________
NS ________
refused ________

Predisposing health conditions

Script for question 20: I'm now going to ask you some general questions about your_ health. I'll be asking about health conditions you_ might have had before [cases: the month before you got sick, in] [month, year of case onset].

20. DID you_ have any of the following health conditions before [cases: the month before you got sick, in] [month, year of case onset]?

[nospln]

a. An operation to remove your_ spleen?

Yes   No   DK   NS   refused

[compdis]

b. An immune system disease called "complement disorder"

Yes	No	DK	NS	refused

[diabet]

c. Diabetes?

Yes	No	DK	NS	refused

[cancer]

d. Cancer, of any type?

Yes	No	DK	NS	refused

[dialysis]

e. A kidney disease requiring dialysis

Yes	No	DK	NS	refused

[HIV]

f. HIV infection, or AIDS?

Yes	No	DK	NS	refused

[cronhlth]

g. Any other chronic health conditions?

Yes	No	DK	NS	refused

[cronspec]

[If yes] What health conditions? ______________________________

[menfren]

21. a. Do you know of any friends, relatives or acquaintances of yours_ that were sick with meningococcal disease during
[year of case onset]?

Yes	No	DK	NS	refused

[If No/DK/NS/refused, skip to instructions following question 21 b below]

[mencont]

b. Were_you living with this person, or, were_you ever in the same room as this person, at any time during [cases: the month before you got sick, in] [month, year of case onset]?

Yes	No	DK	NS	refused

[skip to script for question 27 ON PAGE #9, if [age at onset] is 18 years or more]

[skip to script for question 26 on page #9 if [age at onset] is 5-17 years inclusive]

Breastfeeding

I'm now going to ask you some questions about breastfeeding and care of your child.

22. Was your child ever breastfed?

Yes	No	DK	NS	refused

[If no/DK/refused, skip to question 24 a. below]

[breastfd]

23. At what age, in months, was breastfeeding stopped for your child?

age in months	DK	NS	refused

[breastst]

Daycare

[smkpreg]

24. a. Did the child's mother ever smoke while she was pregnant?

Yes No DK NS refused

b. During [year of case onset], did your child go to daycare, preschool, a child day home, or, participate in an organized play group?

Yes No DK NS refused

[If no/DK/refused, skip to question 26 below]

[daycare]

24 c. Did your child go to daycare, preschool, a child day home, or, participate in an organized play group, during
[cases: the month before you got sick, in] [month, year of case onset]?

Yes No DK NS refused

[If no/DK/refused, skip to question 26 below]

[dcweek]

25. In [cases: the month before you got sick, in] [month, year of case onset], did your child go to daycare, preschool, a child day home, or participate in an organized play group, at least once per week?

Yes No DK NS refused

Maternal Education

[momedu]

26. What is the highest level of education that your child's mother completed? Please choose from the following 8 options:

Grade school ____________
Some high school ____________
High school graduate ____________
Technical school ____________
Some university or college ____________
University or college degree ____________
Graduate university degree ____________
Other (specify) ______________________________________
NS ____________
DK ____________
refused ____________

Aboriginal status (all)

[aborig]

27. Are_you an Aboriginal person, that is, North American Indian, Treaty Indian, Metis, or Inuit?

_________ Yes _________ No _________ DK _________ refused

Income (all)

[income]

28. I'm now going to ask you about your_ household income for [year of case onset], which is the total amount of money made by everyone living in your_ home during [year of case onset]. Which of the following categories best describes the total household income for your_ home before taxes in [year of case onset]?

$15,000 or less __________
15,000-30,000 __________
30,000-45,000 __________
45,000-60,000 __________
More than 60,000 __________
DK __________
NS __________
refused __________

Smoking, passive (all)

Question 29 script: I'm now going to ask you some questions about second hand tobacco smoke. First, I'm going to ask you about the smoking habits of people that live~ in your_ home.

[DECEASED CASES SKIP TO QUESTION 29b BELOW]

29. a. Other than you_, does anyone that lives in your_ home right now ever smoke cigarettes, cigars, or from a pipe?

________ Yes ________ No ________ DK ________ NS ________ refused

b. Other than you_, did anyone that lived in your_ home anytime during [year of case onset] ever smoke cigarettes, cigars or a pipe?

________ Yes ________ No ________ DK ________ NS ________ refused

[If no/DK/refused and participant is DECEASED case, skip to Q34a.]

[If no/DK/refused, [AND case participant is NON DECEASED], AND >12 AND <18 years old during of qtre administration, skip to QUESTION 33]

[If no/DK/refused, [AND case participant is NON DECEASED], and participant is <12 years OR >18 years of age, skip to QUESTION 34 a.]

c. Would you say that the people other than you_ that lived in your_ home during [year of case onset] that were smokers, were smokers during the entire year?

________ Yes ________ No ________ DK ________ NS ________ refused

[psmkhs]

d. Would you say that the people other than you_ that lived in your_ home during [year of case onset] that were smokers, were smokers during [cases: the month before you got sick, in] [month, year of case onset]?

________ Yes ________ No ________ DK ________ NS ________ refused

[psmkwho]

30. I'm now going to ask you whether or not certain people were living in your_ home in [cases: the month before you got sick, in] [month, year of case onset], and, if they did live in your_ home, whether or not they were smokers in [cases: the month before you got sick, in] [month, year of case onset]. Which of the following people lived in your_ home during [cases: the month before you got sick, in] [month, year of case onset]?
As I read off each person, please indicate yes or no.

(Checkmark affirmative responses)	lived there?	Smoker?
Your_ mother	_______	_______
Your_ father	_______	_______
Your_ roommate	_______	_______
Your_ husband, wife, boyfriend or girlfriend	_______	_______
Your_ son or daughter	_______	_______
Your_ brother or sister	_______	_______
Other relative or friend	_______	_______
DK	_______	_______
NS	_______	_______
refused	_______	_______

[psmkhs#]

31. So, the total number of people living in your_ home during [cases: the month before you got sick, in] [month, year of case onset] that smoked, other than you_, was how many?

_______ (total number of smokers)   _______ DK   _______ NS   _______ refused

[psmkmom]

32. Did any of the smokers other than you_ that lived in your_ home during [cases: the month before you got sick, in] [month, year of case onset] smoke inside the home?

_______ Yes   _______ No   _______ DK   _______ NS   _______ refused

[Deceased cases, skip to Question 34 a]

[Participants <12 years or >18 years of age during qtre administration skip to Question 34 a]

33. [ADOL SCRIPT]

[For parents of cases or controls 12-17] I would now like to DIRECTLY ask a few questions of your child, in private. Could you please ask [name of child] to come to the phone, and then could I ask that you go to a place where you cannot hear the answers your child gives?
[When person of interest comes to phone]. OK, like we talked about, I'm going to ask you some questions. Many of my questions will ask that you please think back in time [time elapsed since case onset], to [cases: the month before you got sick, in] [month, year of case onset]. Now it may be difficult for you to remember specific things from that time, so I'm only looking for you to remember as best you can, OK? Remember that you don't have to answer any question you don't want to. I'm going to start by asking you some questions about second-hand smoke.

34. a. Has~ there ever been a time in `your` life when `you` visited places outside `your` home where other people were smoking, more than once in a month?

Yes No NS DK refused

[If No/DK/refused, skip to question 35a below]

b. Would you say that the year [year of case onset] was a time in `your` life when `you` visited places outside `your` home where other people were smoking, more than once in a month?

Yes No NS DK refused

[if No/DK/refused, skip to question 35a below]

[psmkout]

c. Would you say that
[cases: the month before you got sick, in] [month, year of case onset] was a time in `your` life when `you` visited places outside `your` home where other people were smoking, at least once per month?

Yes No NS DK refused

[If No/DK/refused, skip to question 35a below]

[psmkwek]

d. Would you say that
[cases: the month before you got sick, in] [month, year of case onset] was a time in `your` life when `you` visited places outside `your` home where other people were smoking, at least once per week?

Yes No NS DK refused

[DECEASED cases skip to question 36 below]

[psmkchg]

35. a. Now, I want you to think back to
[year of case onset]. Would you say that now, `you` spend_ more, less, or the same amount of time in places outside `your` home where other people were smoking, than `you` did in [cases: the month before you got sick, in] [month, year of case onset]?

More same less NS DK refused

[If [age at onset] is <12 years of age, skip to Script for question 42 below]

<u>Smoking (active)</u>

Question 36 Script: I'm now going to ask you some questions about smoking.

[smkever]

36. Have~you ever smoked~ at least one cigarette?

Yes No NS DK refused

[If no/DK/refused, skip to question 41 on below]

36.a. Has~ there ever been a time in your~ life when you~ smoked cigarettes more than once in a month?

Yes No NS DK refused

[If no/DK/refused, skip to question 39b below]

[smkmnth]

36. b. Would you say that
[cases: the month before you got sick, in] [month, year of case onset] was a time in your~ life when you~ smoked cigarettes more than once in a month?

______ Yes ______ No ______ NS ______ DK ______ refused

37. Has~ there ever been a time in your~ life when you~ smoked cigarettes on most days?

______ Yes ______ No ______ NS ______ DK ______ refused

[If no/DK/refused, skip to question 39 b below]

[smkdaily]

38. Would you say that [cases: the month before you got sick, in] [month, year of case onset] was a time in your~ life when you~ smoked cigarettes on most days?

______ Yes ______ No ______ NS ______ DK ______ refused

[If no/DK/refused, skip to question 39 b below]

[smknum]

39. a. During [cases: the month before you got sick, in] [month, year of case onset], on average, how many cigarettes, or how many packs of cigarettes, would you guess THAT you~ smoked each day?

______ # of cigarettes OR ______ # of packs */20=* ______ *#cigarettes*

[DECEASED cases skip to question 40 below]

[smkchng]

39. b. Now, I want you to think back to
[year of case onset]. Would you say that now, you smoke cigarettes more often, less often, or equally as often, as you did in [cases: the month before you got sick, in] [month, year of case onset]?

______ More ______ less ______ equal ______ NS ______ DK ______ refused

40. a. Have~you ever shared~ the same cigarette with someone else?

Yes	No	NS	DK	refused

[If no/DK/refused, skip to question 41 a. below]

[smkshre]

40 b. Would you say that you~ shared at least one cigarette with someone in [cases: the month before you got sick, in] [month, year of case onset]?

Yes	No	NS	DK	refused

[ntobac]

41. a. Have~you ever smoked~ or inhaled~ something other than tobacco?

Yes	No	NS	DK	refused

[Controls: If no/DK/refused, skip to question 43 below]

[Cases: If no/DK/refused, skip to script for question below]

41 b. Has~ there ever been a time in your~ life that you~ smoked or inhaled something other than tobacco, more than once in a month?

Yes	No	DK	NS	refused

[If no/DK/refused, skip to question 42 below]

[ntobacex]

c. Would you say that
[cases: the month before you got sick, in] [month, year of case onset] was a time in your~ life when you~ smoked or inhaled something other than tobacco more than once in a month?

Yes	No	DK	NS	refused

[If no/DK/refused, skip to question 42 below]

d. When you~ smoked or inhaled something other than tobacco in [cases: the month before you got sick, in] [month, year of case onset], did you~ usually inhale from the same cigarette, pipe or vessel as someone else?

Yes	No	DK	NS	refused

[Controls skip to question 43 below]

Drink, utensil sharing/kissing (all)

Script for question 42: I'm now going to ask you some questions about some of `your`
personal habits. Again, you have the right not to answer any of these questions.

42. During in [cases: the month before you got sick, in] [month, year of case onset], did `you`:

[shrcup]

a. Share a beverage or drink from the same cup or glass as someone else without washing it first?

Yes	No	DK	NS	refused

[shrdrnk]

b. Drink from the same straw, bottle or can as someone else?

Yes	No	DK	NS	refused

[shruten]

c. Use the same fork, knife or spoon as someone else without washing it first?

Yes	No	DK	NS	refused

[shrtbr]

d. Use the same toothbrush as someone else?

Yes	No	DK	NS	refused

[shrlip]

e. share the same lipstick or lip balm as someone else?

_____ Yes   _____ No   _____ n/a   _____ NS   _____ DK   _____ Refused

Script for Question 43: I'm now going to ask you about numbers of people you_have kissed during specific time periods.

[DECASED cases skip to question 44 a below]

43. During the last 30 days, did `you` kiss anyone on the lips?

_____ Yes   _____ No   _____ DK   _____ NS   _____ refused

[kiss]

44. a. Now I want you to think back, to [cases: the month before you got sick, in] [month, year of case onset]. During
[cases: the month before you got sick, in] [month, year of case onset], would you say that `you` kissed anyone on the lips?

_____ Yes   _____ No   _____ DK   _____ NS   _____ refused

[If no/DK/refused, skip to script for question 45 below]

[kissnum]

b. About how many people would you say `you` kissed on the lips during
[cases: the month before you got sick, in] [month, year of case onset]?

_____ # of people   _____ DK   _____ NS   _____ refused

<u>Crowded public areas (all)</u>

Script for question 45: I'm now going to ask you about public places THAT `you` went
to during [year of case onset]

45. a. Has~ there ever been a time in `your` life when `you` sometimes rode the bus or LRT?

Yes No DK NS refused

[If no/DK/NS/refused, skip to question <u>46a</u> below]

[bus]

b. Would you say that in
[cases: the month before you got sick, in] [month, year of case onset] `you` took the bus or LRT?

Yes No DK NS refused

[church]

46. a. Did `you` attend a service at a church, synagogue or mosque in [year of case onset]?

Yes No DK NS refused

[If no/DK/NS/refused, skip to question <u>47a</u> below]

b. Would you say that `you` attended a service at a church, synagogue or mosque in [cases: the month before you got sick, in] [month, year of case onset]?

Yes No DK NS refused

[physact]

47. a. Did `you` participate in team sports or organized physical activity in the year [year of case onset]?

Yes No DK NS refused

[If no/DK/NS/refused, skip to instructions immediately following question 47b below]

b. Would you say that `you` participated in team sports or organized physical activity in [cases: the month before you got sick, in] [month, year of case onset].

Yes No DK NS refused

[If [age at onset] <12 years of age, skip to ENDSCRIPT on page 25]

Youth-oriented crowded public areas

I'm now going to ask you about some other public places.

[rave]

48. a. Have~you ever been~ to a rave?

_____ Yes   _____ No   _____ DK   _____ NS   _____ refused

[If no/DK/NS/refused, skip to question 49a below]

b. Did you~ go to a rave in the year
[year of case onset]?

_____ Yes   _____ No   _____ DK   _____ NS   _____ refused

[If no/DK/NS/refused, skip to question 49a below]

[raveex]

c. Would you say you~ went to a rave during
[cases: the month before you got sick, in] [month, year of case onset]?

_____ Yes   _____ No   _____ DK   _____ NS   _____ refused

[party]

49. a. Did you~ go to a party, such as a hall party or a house party, in
[cases: the month before you got sick, in] [month, year of case onset]?

_____ Yes   _____ No   _____ DK   _____ NS   _____ refused

[gather]

b. Did you~ go to a wedding or extended family gathering outside your~ home in
[cases: the month before you got sick, in] [month, year of case onset]?

_____ Yes   _____ No   _____ DK   _____ NS   _____ refused

[If [age at onset] 16 years of age or greater, skip to question 50a below]

[Participants >12 and <16 years of age at onset]. That's all the questions I have for you. Thank you very much for participating. Do you have any questions? Could I talk to your parent again? [Skip to ENDSCRIPT on page 25]
[bar]

50. a. Has~ there ever been a time in your~ life when you~ visited bars or other establishments where alcoholic drinks are served, more than once in a month?

Yes   No   DK   NS   refused

[If No/DK/NS/refused, skip to question 50c below]

[barex]

b. Would you say that
[cases: the month before you got sick, in] [month, year of case onset] was a time in your~ life when you~ visited bars or other establishments where alcoholic drinks are served, more than once in a month?

Yes   No   DK   NS   refused

[DECEASED cases skip to question 51, below]

[barchng]

c. Now, I want you to think back to the year
[year of case onset]. Would you say that now, you visit bars or other establishments where alcoholic drinks are served, more often, less often, or equally as often, as you did in [cases: the month before you got sick, in] [month, year of case onset]?

More   same   less   NS   DK   refused

Residence at College/university campus housing (16 and older at onset)

[college]

51. During [cases: the month before you got sick, in] [month, year of case onset], did you~ go to college or university classes?

Yes   No   NS   DK   refused

[If no/DK/refused, skip to question 53 below]

[collres]

52. During [cases: the month before you got sick, in] [month, year of case onset], did you~ live in student residence at your_ university or college?

________ Yes	________ No	_____ NS	________ DK	________ refused

53. a. Were~you working in a lab during [cases: the month before you got sick, in] [month, year of case onset]?

________ Yes	________ No	_____ NS	________ DK	________ refused

[If no/DK/refused, skip to question 54 below]

[labex]

53. b. Were meningococcal bacteria were sometimes analyzed in this lab?

________ Yes	________ No	_____ NS	________ DK	________ refused

Life events/stress (16 and older at onset)

[stress]

54. Now I want you to think back to [year of case onset], and think about how much stress or pressure there was in your~ life. In [cases: the month before you got sick, in] [month, year of case onset], which one of the following four choices describes how much stress or pressure there was in your~ life?

Little or no stress	________
SOME stress	________
Very stressful, but not too much to handle	________
So much stress that you~ had trouble dealing with it	________
DK	________
NS	________
refused	________

ENDSCRIPT

[If case 12-17 years old]. That's all the questions I have for you. Thanks very much for taking part in the study. Could I please talk to your parent again? [When parent returns to phone]. Thank you, I have completed my questions with your child, I have one last question for you before I let you go].

[Cases, skip to question #55 below]

[Endscript Controls] This completes my questions. Thank you very much for your participation. If you'd like, I can give you the telephone number of someone to call if you have questions about meningococcal meningitis, or if you have questions or concerns about this study, or if would like the results of this study when they are available in about a year. Would you like to take down the numbers? [If yes] For questions about meningococcal disease, please contact Dr. Marcia Johnson with Capital Health, at 413-7601. For questions about the study, or for information on how to receive THE results of the study, please contact Dr. Colin Soskolne, at 492-6013. If you have any concerns with how this study is being conducted, please contact Dr. Sharon Warren of the University of Alberta Health Research Ethics Board, at 492-7856.

Do you have any questions before I let you go?

Thank you for your valued participation. Goodbye.

Sequelae questionnaire, cases only

[caseaddy]

55. Capital Health would like to mail you a questionnaire regarding your_ meningococcal infection. This questionnaire will ask about symptoms that you_ had because of your_ meningococcal infection. Again, you are in no way obligated to complete this questionnaire.

    May I have your current mailing address?

    [If participant refuses, skip to Endscript BELOW]

    ____

    (case mailing address)

[Endscript Cases]: This completes my questions. Thank you very much for your participation. If you'd like, I can [give you the telephone number/include the phone number in the mail out] of someone to call if you have questions about meningococcal disease, if you have questions or concerns about this study, or if you would like the results of this study when they become available in about a year. Would you like to take down the numbers/shall I include the phone numbers in the mail out?

[If yes] For questions about meningococcal disease, please contact (available MOH) with Capital Health, at 413-7600. For questions about this study, or for information on how to receive the results of this study, please contact Dr. Colin Soskolne, at 492-6013. If you have any concerns with how this study is being conducted, please contact Dr. Sharon Warren of the University of Alberta Health Research Ethics Board, at 492-7856.

Do you have any questions before I let you go?

Thank you. Goodbye.

[UPSET SCRIPT] You sound like you might be upset. Are you able to continue with this interview?

[If Yes]. OK, when you're ready, I will continue. [Skip to counseling script].

[If No]. That's fine. I am now stopping the interview. [Proceed to counseling script].

[Counseling script].

[For cases or parent/guardian of cases]. If you would like, I can ask Capital Health-Public Health Division to contact your physician to refer you to a psychologist. Would you like me to do this?

[If yes] I will make the call to Capital Health. [If participant initially indicated that they weren't able to continue, state: Thank you for your time. Goodbye]. Are you ready to continue? [If yes, return to interview]. OK, let me know when you're ready [return to questioning when participant indicates HE/SHE IS ready].

[For loved ones of fatal cases]. If you would like, I can provide you with a phone number to contact for the names of community groups that sponsor grief counselling services. Would you like to take down the number? [If yes] The name of the organization is "InformEdmonton", and you can reach them at 482-4636. Are you ready to continue? [If yes, return to interview]. OK, let me know when you're ready [return to questioning when participant indicates HE/SHE IS ready].

Appendix I:

Modified Capital Health invasive meningococcal disease information collection sheet

Capital Health

Community Care and Public Health
Public Health Division

INVASIVE MENINGOCOCCAL DISEASE

NDR#

CASE HISTORY

Date Reported to CHA ___ YR ___ MO ___ DAY	*Last Name*	*First Name*	*Date of Birth* ___ YR ___ MO ___ DAY

Sex ☐ Male ☐ Female ☐ Unknown	*Lab Diagnosis* ☐ Yes ☐ No ☐ Pending	*Deceased* ☐ Yes ☐ No ☐ Unknown	*Date of Onset* ___ YR ___ MO ___ DAY ☐ Unknown

Type of Lab Specimen (Check all that apply) ☐ Stool ☐ Urine ☐ Blood ☐ Nose/Throat ☐ CSF ☐ Other ____________________

DISEASE HISTORY

TYPING ___ ___	*One or more of the following symptoms: fever, headache, nausea, vomiting, stiff neck, rash, cough, seizures, coma* ☐ Yes ☐ No ☐ Unknown ☐ Other ____________	*Diagnosis* ☐ Meningitis ☐ Meningococcemia ☐ Pneumonia	*Previously Immunized* ☐ Yes ____________ Date ☐ No ☐ Unknown

Appendix J:

Descriptive risk factor information from study questionnaire for categorical and continuous variables

Descriptive Analysis of Categorical Variables (Variables exhibiting complete separation are underlined)

Variable[*]	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Lived in Canada entire life	3	7	1	0	1	32
Overnight stay away from home	6	12	11	2	9	4
International travel	3	0	5	0	36	0

[*] During month of interest.

[†] The first symbol of each set represents the case in the triad, the next two symbols represent the two matched controls. Exposure is represented by a "+", lack of exposure by a "-". This applies to all tables in this Appendix.

Variable[*]	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Snores while sleeping	7	6	7	3	20	1
Referred to speech therapist prior to month of interest	1	0	5	0	38	0

[*] During month of interest unless otherwise specified.

Variable[*]	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Shared bedroom	6	8	11	3	11	5
Home heating type:						
Furnace	1	5	4	5	0	29
Radiant	5	3	4	2	30	0
Wood	1	0	0	0	43	0
Other	1	0	1	0	42	0
Humidifier on furnace	3	3	15	6	11	6
Other humidifier used in home	4	2	12	3	23	0
Wood fireplace in home	5	5	14	3	14	3
Dust-generating home renovations	0	0	8	0	36	0

[*] During month of interest.

Variable*	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Vaccine-mediated immunity	3	2	4	4	25	6
Asplenia	0	0	0	0	44	0
Complement disorder	0	0	0	0	44	0
Diabetes	2	0	1	0	41	0
Cancer	0	0	4	1	39	0
Kidney disorder requiring dialysis	0	0	0	0	44	0
HIV or AIDS	0	0	0	0	44	0
Other chronic health condition	2	1	16	2	21	2

*Prior to month of interest.

Variable*	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Ever breastfed	0	1	0	0	36	7
Mother smoked while pregnant with participant	2	2	0	0	40	0
Attended daycare, preschool, child day home or organized play group	0	3	1	1	38	1
Attended daycare, preschool, child day home or organized play group at least once per week	0	3	1	1	38	1
Mother of participant did not complete high school[‡]	3	1	2	0	38	0

*During month of interest, unless otherwise specified. Asked only of those <5 years of age at onset, unless otherwise specified.
[‡]asked only of those <18 years of age at onset.

Variable	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Aboriginal person	1	0	3	1	39	0
Household income <$15,000 annually*	3	1	4	0	36	0

*During calendar year that included the month of interest.

Variable*	Matched Sets†					
	+--	+-+/++-	--+/-+-	-++	---	+++
Lived with smoker	8	8	16	2	8	2
Lived with smoker of following category:						
-mother	7	4	3	1	29	0
-father	4	3	10	1	26	0
-roommate	2	0	2	0	40	0
-husband, wife, boyfriend or girlfriend	3	0	5	0	36	0
-son or daughter	0	0	4	0	40	0
-brother or sister	4	0	6	0	34	0
-other relative/friend	2	0	2	0	40	0
Lived with smoker that smoked inside the home	7	5	10	2	20	0
Visited place(s) outside the home where other people smoking	6	12	3	3	4	16
Visited place(s) outside the home where other people smoking at least once per week	8	12	8	3	7	6

*During month of interest.

Variable*	Matched Sets†					
	+--	+-+/++-	--+/-+-	-++	---	+++
Smoked cigarettes at least once per month	5	7	8	1	23	0
Smoked cigarettes on most days	4	6	9	1	24	0
Shared a cigarette	4	7	6	2	25	0
Smoked/inhaled something other than tobacco	6	3	7	0	28	0
Shared pipe/vessel when smoking something other than tobacco	5	3	6	0	29	0

*During month of interest. Asked only of those ≥12 years of age or older at onset.

Variable*	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Kissed someone on lips	6	9	6	3	0	20
Took the bus	6	5	11	3	4	15
Attended a service at a church, synagogue or mosque	4	6	18	10	4	2
Participated in organized physical activity	5	4	18	2	13	2
Attended a party	3	9	4	4	15	9
Attended wedding or extended family gathering outside the home	3	2	9	2	27	1

*During month of interest.

Variable*	Matched Sets[†]					
	+--	+-+/++-	--+/-+-	-++	---	+++
Attended a rave[‡]	7	1	3	0	33	0
Went to a bar or other establishment where alcoholic drinks served	6	10	0	1	20	7
Attended college or university	1	4	8	0	30	1
Lived in student residence at college or university	0	0	1	0	33	0
Worked at a lab where meningococcal bacteria analyzed	0	0	1	0	33	0
Stress level "very stressful" or "so much stress had trouble dealing with it"	3	8	10	2	19	2

*During month of interest. Asked only of those ≥16 years of age or older at onset, unless otherwise specified

[‡] Asked only of those ≥12 years of age or older at onset.

Descriptive Analysis of Continuous Variables

Variable	Cases			Controls		
	Mean	Min	Max	Mean	Min	Max
Yearcan	38.5	33	44	18.1	2	50
Bednum	3.25	1	6	3.49	1	8
Resnum	3.66	1	6	3.86	2	8
Res10*	1.86	1	3	1.67	1	4
Density	1.07	0.33	2.00	1.10	0.40	4.00
Otbednum	1.48	1	3	1.42	1	3
Breastst*	4.85	1	11	11.07	1	36
Psmkno*	1.63	1	4	1.33	1	4
Smknum*	10.6	2	20	12.6	3	25
Kissnum*	2.40	1	10	2.98	1	12

*Among cases with at least one unit of exposure

Variable descriptions:

"yearcan"—of participants that did not report living in Canada for all their life, how long (in years) were they living in Canada before year of onset (cases)/year of onset for matched case (control).

"bednum"—how many bedrooms were there in the participant's home in the month before they got sick (cases)/month of onset of matched case (controls).

"resnum"—including the participant, how many people lived in the participant's home in the month before they got sick (cases)/month of onset of matched case (controls).

"res10"—including the participant, how many people that lived in the participant's home in the month before they got sick (cases)/month of onset of matched case (controls) were less than 10 years of age at that time.

"density"—what was the population density of the participant's home in the month before they got sick (cases)/month of onset of matched case (controls) were less than 10 years of age at that time.

Formula: #residents ≥10 yrs. old + 0.5(#residents <10 years old)/number of bedrooms

"otbednum"—including the participant, how many people regularly slept in the participant's bedroom in the month before they got sick (cases)/month of onset of matched case (controls) were less than 10 years of age at that time.

"breastst"—at what age, in months, was breastfeeding stopped for those participants whose proxy reported that they were ever breastfed.

This question was asked only of participants <5 years of age at onset.

"psmkhsno"—the total number of smokers that lived in the participant's home in the month before they got sick (cases)/month of onset of matched case (controls), of those participants that reported that a smoker lived in the participant's home in the month before they got sick (cases)/month of onset of matched case (controls).

"smknum"— on average, the number of cigarettes, or packs of cigarettes, smoked each day in the month before they got sick (cases)/month of onset of matched case (controls), of those participants that reported that they smoked cigarettes on most days in the month before they got sick (cases)/month of onset of matched case (controls).

This question was asked only of those ≥12 years of age at onset.

"kissnum"— about how many people did the participant reported kissing on the lips in the month before they got sick (cases)/month of onset of matched case (controls), of those participants that reported that they kissed someone on the lips in month before they got sick (cases)/month of onset of matched case (controls).

Appendix K:

Multivariate model building summary

Summary of Multivariate Model Building

(descriptions of the variable names included at any point in the model are included after the last model building step)

1. Model including all variables with a likelihood ratio test p-value less than 0.25, excluding variables exhibiting complete separation.

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Canlife	3.749	2.721	1.897	1	.168	42.465	.205	8801.801
Furnace	-1.089	1.110	.963	1	.327	.336	.038	2.965
Furnhum	-1.679	.962	3.049	1	.081	.187	.028	1.228
Humoth	-4.469	2.077	4.627	1	.031	.011	.000	.672
Immprot	1.906	1.312	2.111	1	.146	6.727	.514	87.983
Diabet	.780	2.487	.098	1	.754	2.181	.017	285.443
Cronhlth	-2.102	1.094	3.692	1	.055	.122	.014	1.043
Breastst	-.263	.285	.853	1	.356	.769	.440	1.343
Momedex	3.123	2.331	1.795	1	.180	22.720	.236	2190.776
Psmkwhom	3.651	1.757	4.320	1	.038	38.523	1.231	1205.335
Psmkhsno	-1.801	.840	4.600	1	.032	.165	.032	.856
Ntobacex	-1.233	2.513	.241	1	.624	.291	.002	40.110
Kiss	1.283	1.037	1.532	1	.216	3.609	.473	27.540
Church	-.801	.782	1.048	1	.306	.449	.097	2.080
Ravemnth	6.666	2.875	5.377	1	.020	785.392	2.805	219695.769
Barex	5.923	2.839	4.353	1	.037	373.421	1.432	97380.720
Passsmk			2.549	2	.280			
Passsmk(1)	1.290	1.261	1.048	1	.306	3.634	.307	43.010
Passsmk(2)	-.505	1.185	.182	1	.670	.603	.059	6.151
Smkmonth	.565	1.212	.218	1	.641	1.760	.164	18.917

2. Model including all variables with a Wald test p-value < 0.05, excluding variables exhibiting instability (i.e. upper limit of 95% confidence interval >> 100).

Variable	β	SE	Wald	Df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Humoth	-.763	.533	2.049	1	.152	.466	.164	1.325
Psmkhsno	.335	.225	2.218	1	.136	1.398	.900	2.173
Immprot	-.479	.622	.593	1	.441	.619	.183	2.096

3. Model including all variables with a Wald test p-value < 0.05, including variables exhibiting instability (i.e. upper limit of 95% confidence interval >> 100). Note: the test statistic used to compare the reduced model below with the full model in #1 above (i.e. likelihood ratio test value for reduced model minus full model) was less than the χ^2 distribution value at 16 degrees of freedom, significance level of 0.05. Thus, the removed variables were not significant predictors.

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Humoth	-1.771	.837	4.472	1	.034	.170	.033	.878
Immprot	.151	.800	.036	1	.850	1.163	.242	5.585
Psmkwhom	3.205	1.100	8.485	1	.004	24.660	2.854	213.110
Ravemnth	2.525	1.068	5.595	1	.018	12.492	1.542	101.230
Barex	3.690	1.295	8.119	1	.004	40.027	3.163	506.487
Psmkhsno	-.562	.381	2.178	1	.140	.570	.270	1.202

4. Variable "Psmkhsno" has insignificant Wald test p-value. Variable removed, and confounding test (Δβ for remaining variables) carried out. Δβ>15%-was observed for some variables, and thus Psmksno was be kept in the final main effects model.

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Humoth	-1.736	.803	4.677	1	.031	.176	.037	.850
Immprot	-.027	.810	.001	1	.974	.974	.199	4.766
Psmkwhom	2.258	.808	7.809	1	.005	9.564	1.963	46.606
Ravemnth	1.841	.881	4.360	1	.037	6.301	1.120	35.459
Barex	3.756	1.417	7.026	1	.008	42.795	2.661	688.159

5. Test for confounding (Δβ for remaining variables) carried out for other variables removed from the model, one at a time. Δβ>15% was observed for at least one variable when "breastst", "momedex" and "passsmk" were added; these were included in the final main effects model.

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Humoth	-2.086	.898	5.395	1	.020	.124	.021	.722
Immprot	-.056	.800	.005	1	.944	.946	.197	4.534
Psmkwhom	2.050	.814	6.336	1	.012	7.764	1.574	38.297
Ravemnth	1.805	.893	4.082	1	.043	6.079	1.056	35.005
Barex	3.762	1.371	7.536	1	.006	43.042	2.933	631.636
Breastst	-.127	.132	.935	1	.333	.880	.680	1.140

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Humoth	-2.400	1.033	5.396	1	.020	.091	.012	.687
Immprot	.101	.835	.015	1	.904	1.106	.215	5.679
Psmkwhom	2.173	.841	6.672	1	.010	8.789	1.689	45.727
Ravemnth	2.159	.992	4.735	1	.030	8.661	1.239	60.535
Barex	3.512	1.268	7.678	1	.006	33.526	2.795	402.106
Momedex	1.695	1.137	2.220	1	.136	5.445	.586	50.605

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Humoth	-1.840	.836	4.837	1	.028	.159	.031	.819
Immprot	.073	.836	.008	1	.931	1.075	.209	5.535
Psmkwhom	2.235	.822	7.394	1	.007	9.346	1.866	46.797
Ravemnth	2.174	.997	4.757	1	.029	8.797	1.247	62.082
Barex	3.863	1.516	6.491	1	.011	47.611	2.438	929.792
Passsmk			1.553	2	.460			
Passsmk(1)	.892	.752	1.409	1	.235	2.441	.559	10.651
Passsmk(2)	.250	.647	.149	1	.699	1.284	.362	4.559

6. Final main effects model

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
humoth	-3.526	1.394	6.400	1	.011	.029	.002	.452
immprot	.411	.826	.247	1	.619	1.508	.298	7.619
psmkwhom	3.568	1.302	7.504	1	.006	35.434	2.760	454.973
ravemnth	4.274	1.614	7.016	1	.008	71.814	3.039	1697.152
barex	3.974	1.364	8.486	1	.004	53.196	3.670	771.027
breastst	-.231	.200	1.330	1	.249	.794	.536	1.175
momedex	2.122	1.324	2.569	1	.109	8.347	.623	111.822
psmkhsno	-.887	.441	4.047	1	.044	.412	.174	.977
passsmk			3.419	2	.181			
passsmk(1)	1.478	.865	2.921	1	.087	4.385	.805	23.887
passsmk(2)	.272	.704	.150	1	.699	1.313	.331	5.215

7. Test for linearity assumption for continuous variables in the model. The minimum, first and second quartile value for both continuous variables is zero; thus, a plot of β versus quartile mid points would not be linear. Thus, both variables do not conform to the linearity assumption.

		Breastst	psmkhsno
	Valid	132	132
	Missing	0	0
Median		.00	.00
Minimum		0	0
Maximum		36	4
	25	.00	.00
	50	.00	.00
	75	.00	1.00

8. As they did not conform to the linearity assumption, continuous variables in the model were replaced with corresponding dichotomous variables (presence/ absence of at least one unit of exposure). The corresponding dichotomous variable for "breastst" was not added, however, as it exhibited complete separation.

Variable	β	SE	Wald	df	Sig.	Exp(β)	95.0% CI for Exp(β)	
							Lower	Upper
Humoth	-2.787	1.159	5.779	1	.016	.062	.006	.598
Immprot	.199	.876	.052	1	.820	1.220	.219	6.792
Psmkwhom	3.161	1.048	9.104	1	.003	23.594	3.027	183.893
Ravemnth	3.165	1.195	7.015	1	.008	23.686	2.277	246.388
Barex	3.857	1.341	8.272	1	.004	47.331	3.417	655.676
Momedex	1.989	1.200	2.745	1	.098	7.306	.695	76.805
Passsmk			2.771	2	.250			
Passsmk(1)	1.248	.836	2.229	1	.135	3.483	.677	17.917
Passsmk(2)	.150	.731	.042	1	.838	1.162	.277	4.870
Psmkhs	-1.283	.681	3.548	1	.060	.277	.073	1.053

9. Tests for five plausible interactions among this model were carried out:

- psmkwhom*momedex
- psmkwhom*psmkhs
- ravementh*barex
- ravementh*passsmk
- barex*passsmk

None of these interactions achieved statistical significance when added to the model one at a time. Thus, the model presented in Step 8 above is the final multivariate model.

"canlife"—had the participant lived in Canada for all of his/her life.

"furnace"—was "furnace" a type of heating in the participant's home (among the choices "furnace, radiator heating pipes, wood, or other") during the month before he/she got sick (cases)/month of onset of matched case (controls).

"furnhum"—was the participant's home heated with a furnace that had a humidifier attached to it during the month before he/she got sick (cases)/month of onset of matched case (controls).

"immprot"—did the participant report receiving the meningococcal meningitis shot before he/she got sick (cases)/month of onset of matched case (controls) AND was he/she sick (cases)/matched case sick (controls) with a vaccine-preventable meningococcal serogroup.

"diabet"—did the participant have diabetes prior to the month he/she got sick (cases)/prior to month of onset of matched case (controls).

"cronhlth"—did the participant have any chronic health conditions (other than the 6 specific health conditions asked about) prior to the month he/she got sick (cases)/prior to month of onset of matched case (controls).

"breastst"—at what age, in months, was breastfeeding stopped for those participants whose proxy reported that they were ever breastfed.

This question was asked only of participants <5 years of age at onset.

"momedex"—was the highest level of education completed by the participant's mother below that of a high school diploma.

This question was asked only of participants less than 18 years of age at onset.

"psmkwhom"—did the participant/proxy report that the participant's mother lived in the participant's home in the month before onset (cases)/month of onset of matched case (controls) and, if the mother did live in the home, that she was a smoker during the month before onset (cases)/month of onset of matched case (controls).

"psmkhsno"—the total number of smokers that lived in the participant's home in the month before they got sick (cases)/month of onset of matched case (controls), of those participants that reported that a smoker lived in the participant's home in the month before they got sick (cases)/month of onset of matched case (controls).

"ntobacex"—did the participant/proxy report that the month before he/she got sick (cases)/month of matched case onset (controls) was a time in his/her life that he/she smoked or inhaled something other than tobacco more than once in a month.

This question was asked only of those >=12 years of age at time of onset.

"kiss"—did the participant/proxy report that he/she kissed someone on the lips in the month before he/she got sick (cases)/month of matched case onset (controls).

"church"—did the participant/proxy report that during the month before he/she got sick/month of onset of matched case (controls) he/she attended a service at a church, synagogue or mosque.

"ravemnth"—did the participant/proxy report that during the month before he/she got sick/month of onset of matched case (controls) he/she had ever been to a rave.

This question was asked only of those >=12 years of age at time of onset.

"barex"—did the participant/proxy report the month before he/she got sick (cases)/month of matched case onset (controls) was a time in his/her life that he/she visited bars or other establishments where alcoholic drinks are served more than once in a month.

This question was asked only of those >=16 years of age at time of onset.

"passsmk".—how often did the participant/proxy report that, in the month before he/she got sick (cases)/month of onset of matched case (controls) he/she visited places outside his/her home where other people were smoking. Trichotomous none, light (≥1/month, <1/week) and heavy (≥1/week) exposure.

"smkmenth"—did the participant/proxy report the month before he/she got sick (cases)/month of matched case onset (controls) was a time in his/her life that he/she smoked cigarettes more than once in a month.

This question was asked only of those >=12 years of age at time of onset.

"psmkhs"—were people other than the participant that lived in the participant's home in the year of onset (cases)/year of onset of matched case (controls) that smoked cigarettes, cigars or from a pipe, smokers during the month before onset (cases)/month of onset of matched case (controls).